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An enantioselective total synthesis of pumiliotoxin 251D

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Award date:
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AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF PUMILIOTOXIN 251D

Submitted by David Nathan Abraham Fox

for the degree of Ph.D.

of the University of Bath

1990

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Acknowledgements

In submitting this thesis, I would like to thank my supervisor, Dr. Timothy Gallagher, for producing such a rewarding project out of the hat when it seemed, at one point, that all had been lost. Since then, his remarkable enthusiasm, encouragement and generosity have contributed in no small manner to an immensely enjoyable and educational time at Bath University. It is appropriate also to extend my gratitude to Dr. David Lathbury for the interest and invaluable advice he has provided over the three years.

I am indebted to the technical staff at Bath University for the efficient and indispensable services they have provided during the course of this work: Mr. Dave Wood and Mr. R.R. (Harry) Hartell (NMR), Mr. Alan Carver (elemental analyses) and Mr. Chris Cryer (mass spectra). The X-ray structure determinations were carried out by Drs. Mary Mahon and Kieran Molloy and I am very grateful for their invaluable contribution. For their smooth running of the stores and for general technical help, my thanks to Mrs. Sue Boucher, Mr. John Bradley and Mr. Russel Barlow as well as to Mrs. June Stainer and Mrs. Freda Smart for their cheerful assistance.

To my colleagues in the organic chemistry department, I am grateful for the intellectual stimulation over the three years and for the friendships I have formed. In particular, I wish to thank Dr. Nick Huby (Noz) for sharing his considerable practical expertise along with his quite unique humour.

I would like to express my gratitude to Mrs. Jo Curtis for her extremely efficient typing undertaken, as always, with a smile. I wish to thank my team of proof-readers for ironing-out those last remaining "typos" and for their willingness to shoulder the blame for any that might still have got away.

Finally, I am grateful to the SERC for a quota award.

To my parents,

for their love and unconditional support.

Summary

This work describes an enantioselective approach to the indolizidine natural product pumiliotoxin 251D, employing an asymmetric electrophile-mediated cyclisation as a key step in the total synthesis.

A review of the isolation, characterisation and biological importance of pumiliotoxin A alkaloids is followed by an account of previous synthetic efforts in this area. A second review describes the achievements, to date, in the field of diastereoface selective interactions of carbon-bond π-systems with metal electrophiles.

A detailed study into the scope of electrophile-mediated cyclisations of allenic amines attached to a range of chiral residues is reported. Dual emphasis is placed on diastereoselectivity and functionality in the cyclised product, focussing initially on silver(I)- and palladium(II)-mediated processes. The disparity in behaviour of these two transformations is rationalised in terms of alternative mechanisms. The potential role of the chiral residue both as an internal resolving agent and as a control element in the cyclisation is discussed and extensions of the methodology are described employing alternative metal- and non-metal-based electrophiles.

The enantioselective approach to optically pure functionalised vinylpyrrolidines forms an integral part of the total synthesis of pumiliotoxin 251D . Efficient elaboration of the product of palladium(II)-mediated cyclisation/carbomethoxylation to the indolizidine skelton and subsequent introduction of a chiral Z-alkylidene side chain *via* an aldol/elimination sequence are crucial to the success of this highly versatile synthesis.

CONTENTS

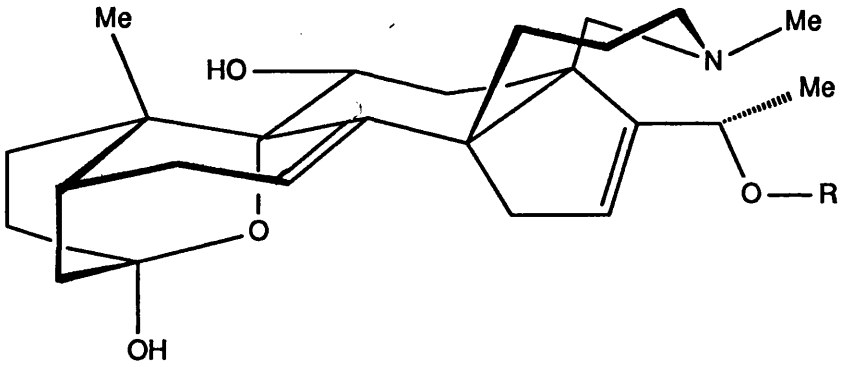
ABBREVIATIONS

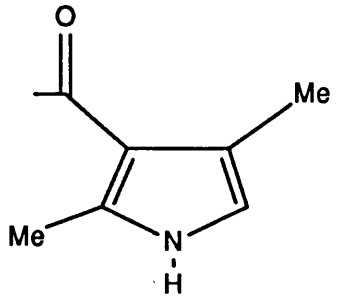
The following abbreviations are used in the text:

Ac	acetyl
AIBN	azobisisobutyronitrile
*t*BDMS	*tert*-butyldimethylsilyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
b.p.	boiling point
br	broad
CHIRAPHOS	bis(diphenylphosphino)butane
C.I.	chemical ionisation
*m*CPBA	*meta*-chloroperbenzoic acid
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodiimide
DiBAl	diisobutylaluminium hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPHOS	1,2-bis(diphenylphosphino)ethane
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulphoxide
E^+	electrophile
E.I.	electron impact
ent	enantiomer
epi	epimer
ether	diethyl ether
eq	equivalents
h	hours
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorato

HOMO	highest occupied molecular orbital
LDA	lithium diisopropylamide
m	meta
M^+	molecular ion
min.	minutes
m.p.	melting point
Ms	methanesulphonyl
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
n	straight chain
n.O.e.	nuclear Overhauser effect
Nu-	nucleophile
o	ortho
p	para
p.p.m.	parts per million
r.t.	room temperature
t	tertiary
TMS	trimethylsilyl
Tf	trifluoromethylsulphonyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
Ts	tosyl, 4-methylphenylsulphonyl
Δ	heat
δ	chemical shift

INTRODUCTION



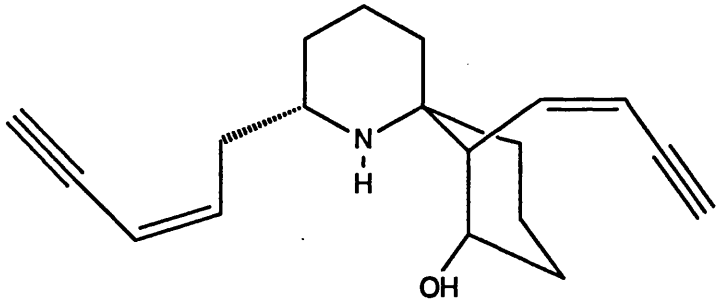


R =

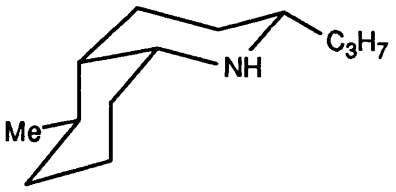
Batrachotoxin **(1)**

R = H

Batrachotoxin A **(2)**



Histrionicotoxin **(3)**



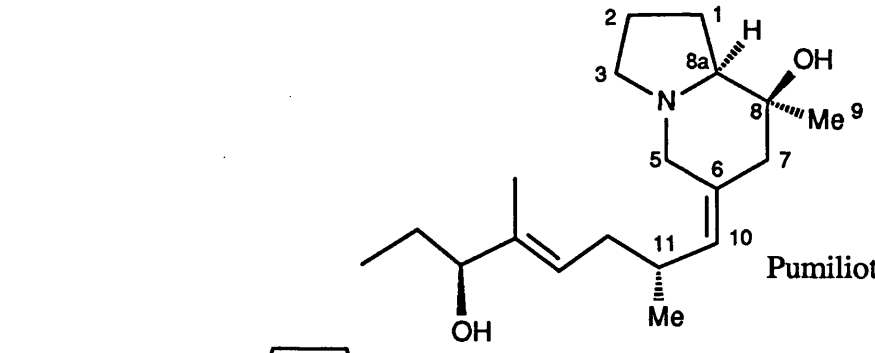
Pumiliotoxin C **(4)**

Figure 1

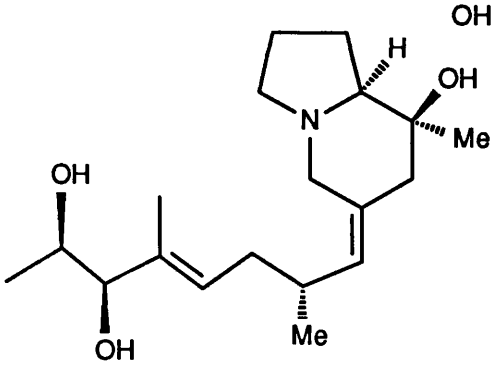
1.1 Pumiliotoxin A Alkaloids - Occurrence and Pharmacology

The neotropical poison-dart frogs are a rich source of biologically active and structurally challenging alkaloids.[1] The use of skin secretions from these amphibians by native South American Indians to poison blow darts is thought to have spanned centuries but the first documented account appeared in 1825.[2] Cochrane's *Travels in Columbia* provides a vivid description of the method by which the venomous substances are extracted from the most potent *Phyllobates* species of this family of frogs *Dendrobatidae*. A spear is passed down the throat, through the body and out at one of the legs; the resulting pain elicits the formation of a white froth on the surface of the skin which contains the most powerful poisons. The species *Phyllobates terribilis*, as its name might suggest, is so efficient at producing highly noxious secretions, that wiping the darts across the back of the living frog is sufficient for envenomation. The venom retains its potency for up to a year and each frog, although only a few centimetres in length, provides enough poison for fifty arrows. The family of frogs consists of over one hundred different members exhibiting a wide ecological diversity. Bright coloration, however, is a common feature and is perhaps an indication of the most likely function of their associated toxins as a defence against predators.

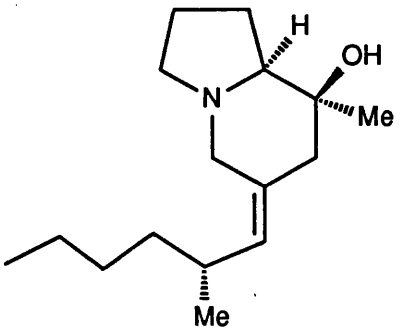
Extraction of the active species present in dendrobatid skin secretions has resulted in the discovery of more than 200 new alkaloids,[3] the structure of many of these being confirmed by total synthesis.[4] They fall into six main classes; the batrachotoxins (the most potent of the alkaloids), the histrionicotoxins, pumiliotoxin C and congeners, the pumiliotoxin A family, the gephyrotoxins and a group of bicyclic indolizidines (Figure 1).



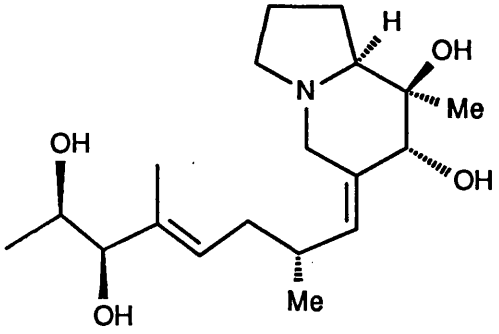
(5)
Pumiliotoxin A (307A′)



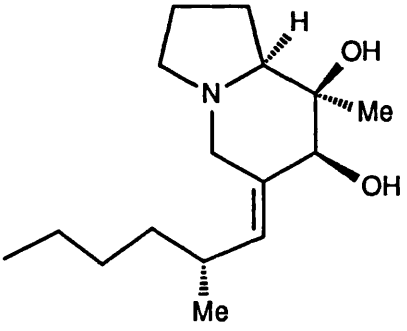
(6)
Pumiliotoxin B (323A)



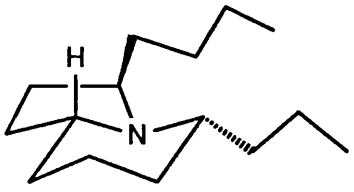
(7)
Pumiliotoxin 251D



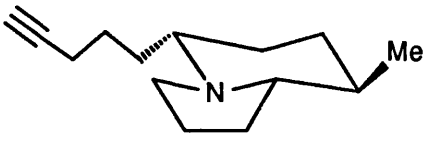
(8)
Allopumiliotoxin 339B



(9)
Allopumiliotoxin 267A



(10)
Gephyrotoxin 223AB



(11)
Indolizidine 205A

Figure 1 (contd.)

Concerted investigation in this area was a consequence of the demonstration that the active principle from one of the poison-dart frogs was an extremely toxic alkaloid.[5] Developments in the study of their pharmacological significance over the succeeding twenty-five years[6] have been mirrored by the refinement of new and versatile chemical synthetic methods aimed at these alkaloids and, more generally, at construction of indolizidine[7] and decahydroquinoline[8] skeletons. This twinned progress is a direct result of the scarcity of the frogs as a natural resource and the elucidation of physiological processes that the alkaloids have promoted. This present discussion focusses on the advances made in the area of the pumiliotoxin A class of alkaloids with respect to their structure determination, biological significance and total synthesis.

Pumiliotoxin A[5] and pumiliotoxin B,[6] first isolated from the Panamanian frog *Dendrobates pumilio* in 1967 were the parent members of this class of alkaloids but their structural elucidation was hampered by an acid-labile side chain. It was as late as 1980 that the long-awaited key to the structural characteristics of this family was provided; the X-ray analysis of a less complex congener indicated the presence of the (Z)-6-alkylideneindolizidine skeleton, common to all the pumiliotoxin A alkaloids.[9] The alkaloid that provided this vital clue was pumiliotoxin 251D (**7**) and although its presence in a number of frog species had been recognised earlier, its significance as the major component of the skin extracts from the Ecuadorian frog *Dendrobates tricolor* was not appreciated initially owing to its remarkable volatility. Extracts from skins of some 750 frogs provided 21mg of the alkaloid and the information derived from the structure of the hydrochloride salt, coupled with mass spectral and NMR data allowed assignment of structures to the more complex analogues,[10] some of which have since been confirmed by total synthesis. Pumiliotoxins A and B are the most potent of the class and although have been shown to be relatively toxic in mice

(LD_{50} 1.5-2.5 mg/Kg), are still at least two orders of magnitude less toxic than the batrachotoxins. A somewhat less potent subclass of the pumiliotoxin A family are the allopumiliotoxins isolated from *Dendrobates auratus* and characterised by an additional hydroxyl functionality at C7 of the indolizidine.

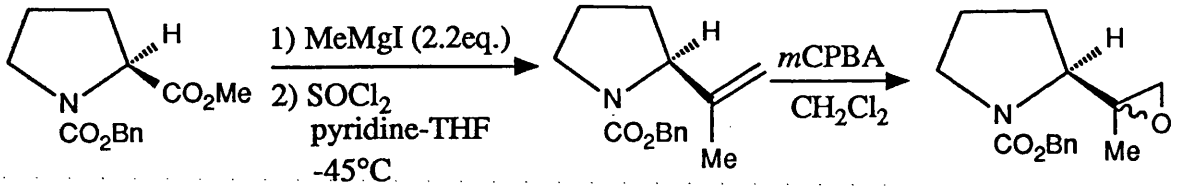
Increased awareness of pumiliotoxin alkaloids has seen a concomitant growth of interest in their use as pharmacological probes for receptor sites and ion channels. Pumiliotoxin B is a representative member of the pumiliotoxin A class of alkaloids and it has been shown to potentiate both direct and indirect evoked contraction of skeletal muscle and prolongs muscle contraction.[6c] This myotonic activity extends to potent cardiotonic properties eliciting both positive chronotropic and inotropic responses. These effects have been shown to be reversible and appear to be linked to a mechanism involving increased calcium influx into the muscle fibre coupled with the facilitation of calcium release from the sarcoplasmic reticulum. It has been proposed that the prolongation of muscle contraction is a result of inhibition of the calcium-dependent ATPase of the sarcoplasmic reticulum. This enzyme is primarily responsible for the re-uptake of calcium ions released into the cytoplasm. There has been shown to be a good correlation between the prolongation of muscle twitch and inhibitory effects on calcium-dependent ATPase promoted by pumiliotoxin B. Pumiliotoxin 251D, however, has been shown to be markedly less active than pumiliotoxin B in terms of myotonic and cardiotonic properties. Indeed, in some experiments it has been shown to have cardiodepressant activity.[6e] Nevertheless, its effect on calcium-dependent ATPase activity was near 100% inhibition (compared with 50% inhibiton by pumiliotoxin B at similar concentrations) and rather less specific, inhibiting sodium/potassium-dependent ATPase as well as magnesium-dependent ATPase.

A more recent and very extensive study of both natural and synthetic

pumiliotoxin B analogues has pointed to an alternative mode of action.[6f,6g,6h,6i] These investigations have demonstrated the pumiliotoxin B-elicited stimulation of sodium flux and phosphoinositide breakdown in guinea pig cerebral cortical synaptoneurosomes. These effects are potentiated by scorpion venom which bind to a sodium ion channel site and delay inactivation. Inactive congeners (eg pumiliotoxin 251D) that lack hydroxyl groups in the Z-alkylidene side-chain, inhibit sodium flux promoted by pumiliotoxin B, scorpion venom or the sodium channel activator batrachotoxin. There is, however, no effect on the binding of [^{3}H]batrachotoxinin-A benzoate to sodium channels. It has been reported previously that agents activating sodium influx have also been shown to stimulate phosphoinositide breakdown in brain synaptoneurosomes.[11]

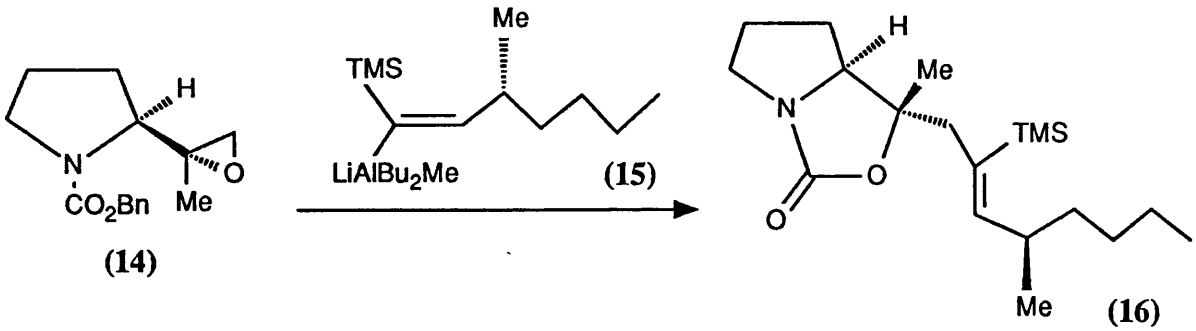
It appears, therefore, that the sodium flux enhancement is a result of interaction with a unique modulatory site on the voltage dependent sodium channels which is allosterically coupled to other binding sites.[6h,6i,12] The ensuing inhibition of inactivation of the channel increases sodium ion flux which in turn stimulates the phosphoinositide breakdown. Phosphoinositides are believed to be important in signal transduction and subsequent generation of second messengers in the central nervous system.[13] It is proposed that the interference with this mechanism is responsible for the myotonic and cardiotonic properties associated with the active pumiliotoxins. Indeed, pumiliotoxins that exhibit a small degree of cardiodepressant activity have minimal effect on phosphoinositol breakdown.

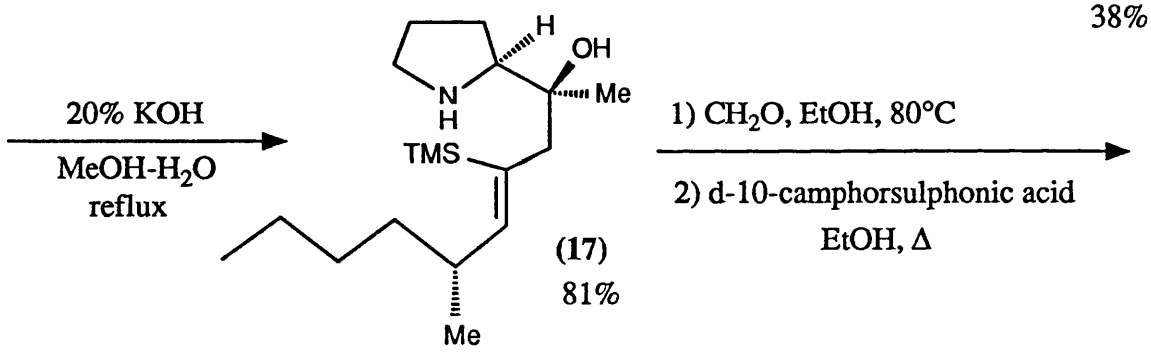
The pumiliotoxin A family would seem to be an important new class of substances for investigation of voltage-dependent sodium channels. For such a role to be fulfilled, versatile and efficient synthetic routes to the natural and unnatural congeners are required and the past decade has seen a series of elegant solutions to the problems posed by their intriguing structures; the remainder of this discussion reviews briefly the achievements in this area to date.

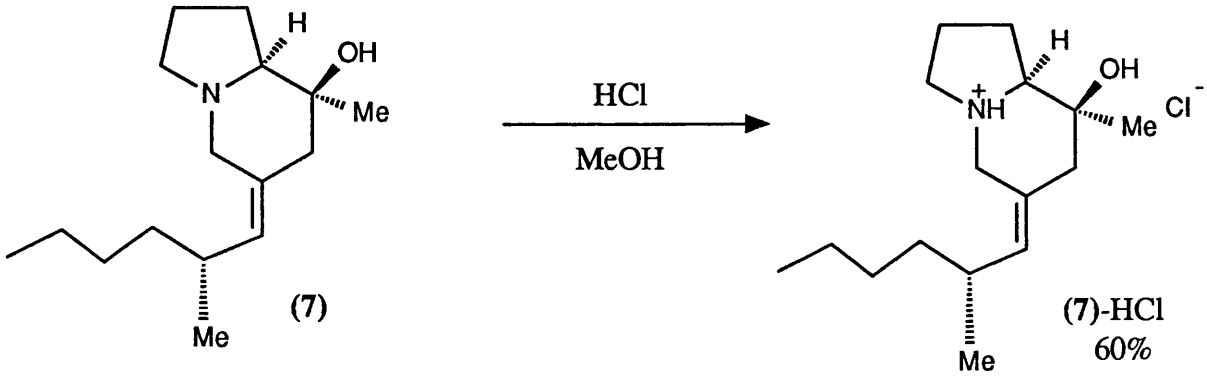


(12) **(13)** 46% **(14)** quantitative yield of 1:1 mixture

Scheme 1





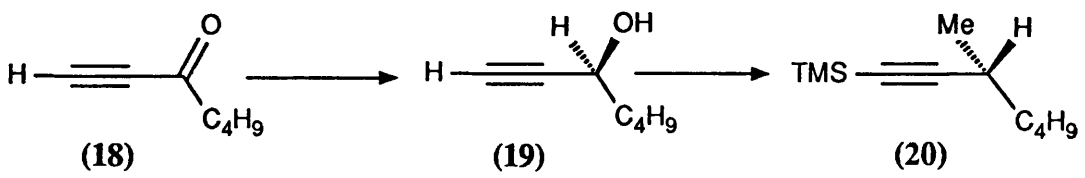


Scheme 2

1.2 Pumiliotoxin A Alkaloids - Synthetic Approaches

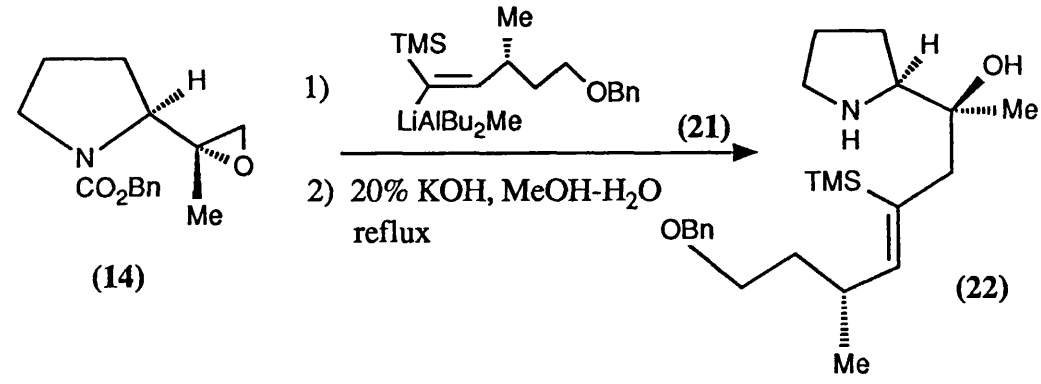
By far and away the major contribution to the development of synthetic methodology aimed at the pumiliotoxin alkaloids has been by Overman and co-workers. His impressive syntheses over the last decade or so have provided elegant and efficient means of introducing functionality in a controlled manner, as well as opening the door to extensive biological studies, with which he has had close association.

In 1981, Overman published the first total synthesis of a pumiliotoxin-A alkaloid.[4a] It was fitting that the target chosen was the first to be structurally-defined: pumiliotoxin 251D (**7**). The synthetic route is shown in Schemes 1 and 2, starting from a proline derivative to introduce, from the outset, the pyrrolidine subunit. A key step in the synthesis is a stereospecific vinylsilane-iminium ion cyclisation to introduce the Z-alkylidene subunit in (**7**). The substrate (**17**) for this transformation is derived from reaction of the appropriate epoxide (**14**) with the chiral vinylaluminium reagent (**15**) followed by basic hydrolysis of the resulting cyclic carbamate (**16**). The reagent (**15**) was obtained by *syn*-hydroalumination of the alkynylsilane (**20**) (Scheme 3) available from (**19**) in three steps and overall 50% yield. (**19**) is the product of stereocontrolled carbonyl reduction of (**18**) according to the method of Midland.[14] The mixture of products (**14**) reflects a lack of diastereoselectivity in the epoxidation reaction of the alkene (**13**), which itself is derived from *N*-carbobenzyloxy-L-proline methyl ester (**12**) in two steps.



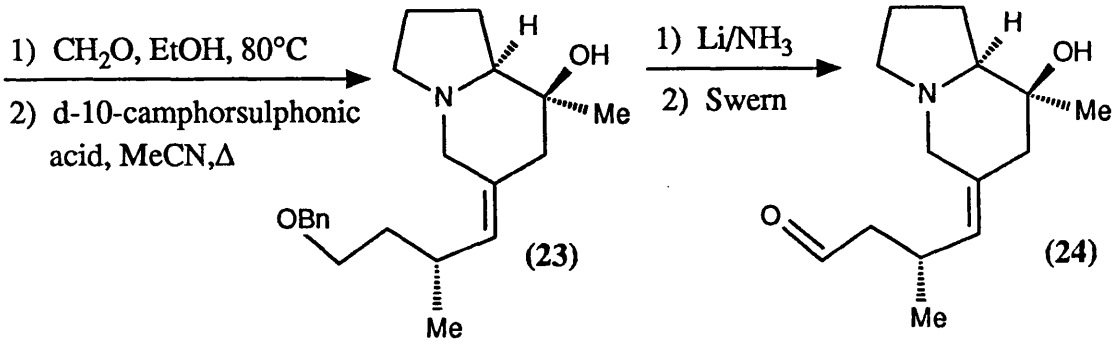
(**18**) (**19**) (**20**)

Scheme 3



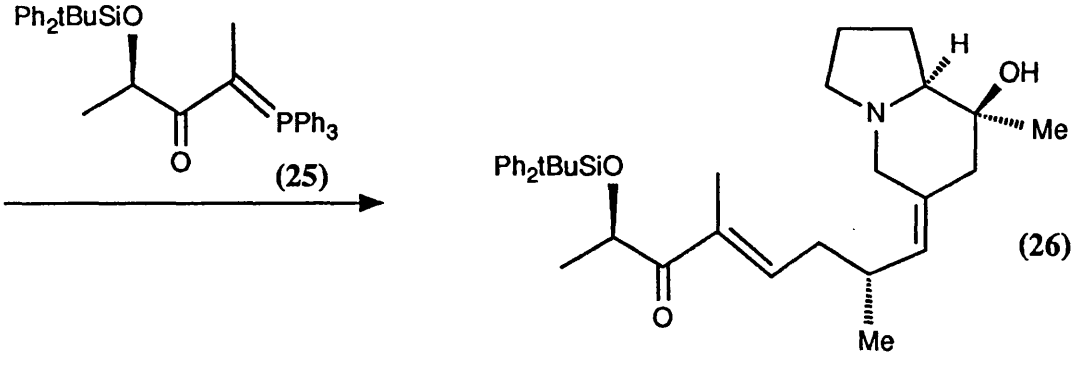
(14)

(22)

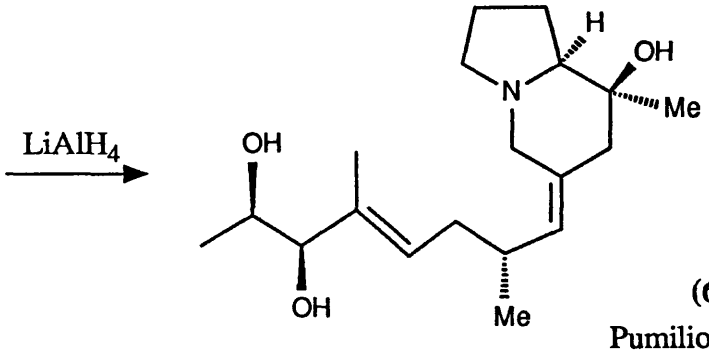


(23)

(24)



(26)



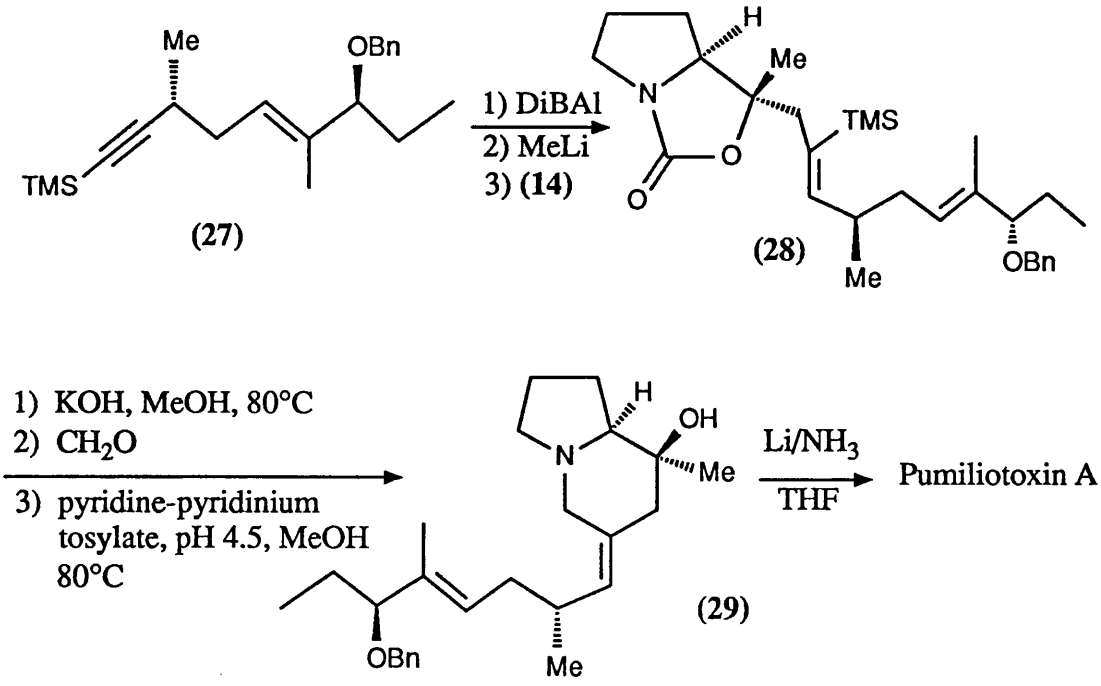
(6)
Pumiliotoxin B

Scheme 4

The synthesis described affords enantiomerically pure (+)-pumiliotoxin 251D hydrochloride in nine steps and 3.6% yield. Its versatility has since been demonstrated by the total syntheses of the more complex pumiliotoxins B and A (Schemes 4 and 5) using similar methodology, serving to establish their structural identities.

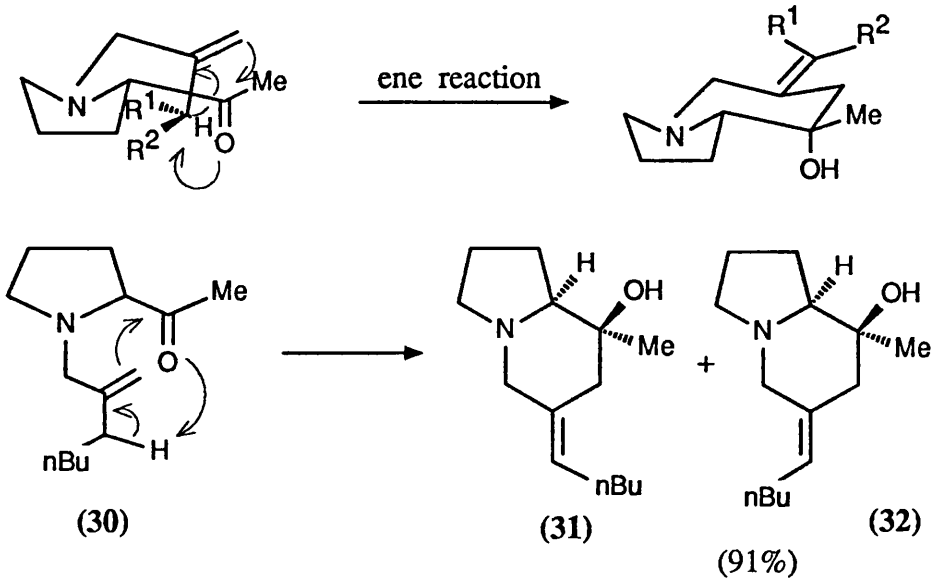
The route to pumiliotoxin B (**6**)[4d] involves synthesis of (**22**), the oxygenated vinylsilane analogue of (**17**) (Scheme 4). Stereospecific cyclisation under similar conditions as previously described afforded, on debenzylation of (**23**) and oxidation, the aldehyde (**24**) which, when combined with ylide (**25**) afforded the E-enone (**26**) exclusively. *Syn*-selective reduction with lithium aluminium hydride was accompanied by desilylation to afford pumiliotoxin B in thirteen steps and overall 1.3% yield.

The approach adopted in the synthesis of pumiliotoxin A (**5**)[4e] was to develop the functionality in Z-alkylidene side chain prior to the hydroalumination-epoxide opening sequence (Scheme 5). This served to demonstrate that the vinylsilane-iminium ion cyclisation was compatible with such functionality. Thus, hydroalumination of (**27**) followed by treatment with methyllithium and then the epoxide (**14**) common to all these syntheses afforded, as previously, the cyclic carbamate (**28**). Basic hydrolysis and reaction of the pyrrolidine with formaldehyde afforded, under carefully buffered conditions, the required iminium ion which underwent stereospecific cyclisation and, on debenzylation, completed this efficient thirteen step synthesis in 5% yield.

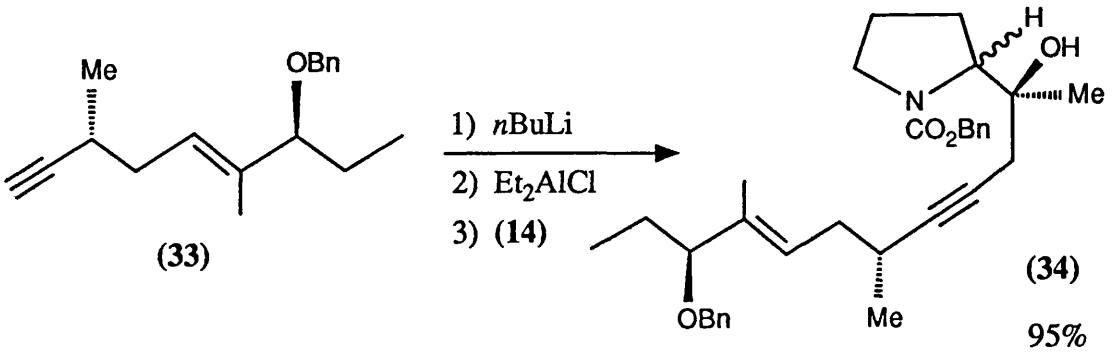


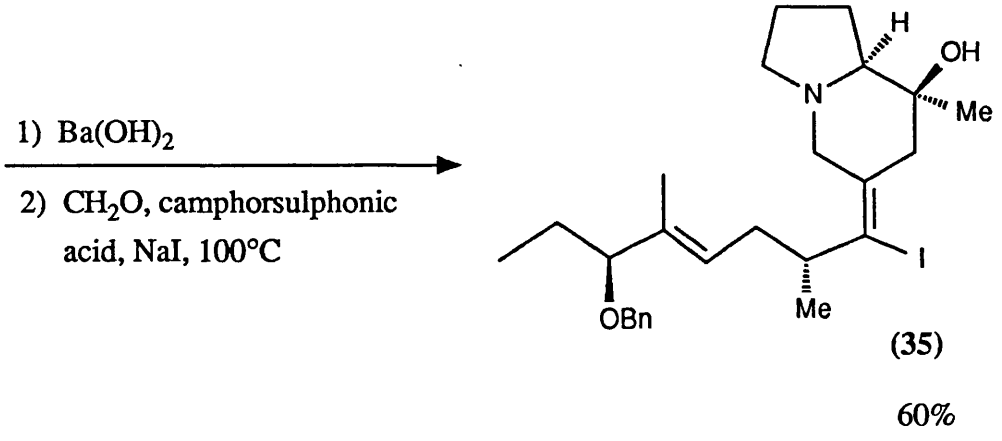
Scheme 5

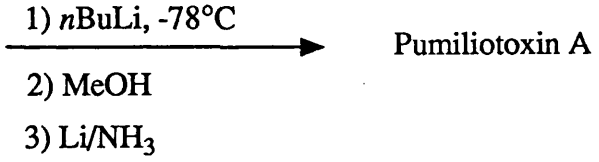
In 1985, Overman, having recognised the axial nature of the tertiary hydroxyl group in the indolizidine skeleton of the pumiliotoxin A alkaloids, published a synthesis of E-alkylidene analogues by intramolecular ene cyclisation (Scheme 6).[7b] Thus, cyclisation of unsaturated ketone **(30)** in the presence of aluminium chloride, afforded, in high yield, a 3:1 mixture of E:Z alkylidene isomers **(31)** and **(32)**.



Scheme 6


Me
OBn
(33)
1) nBuLi
2) Et2AlCl
3) (14)
H
OH
Me
N
CO2Bn
OBn
Me
(34)
95%

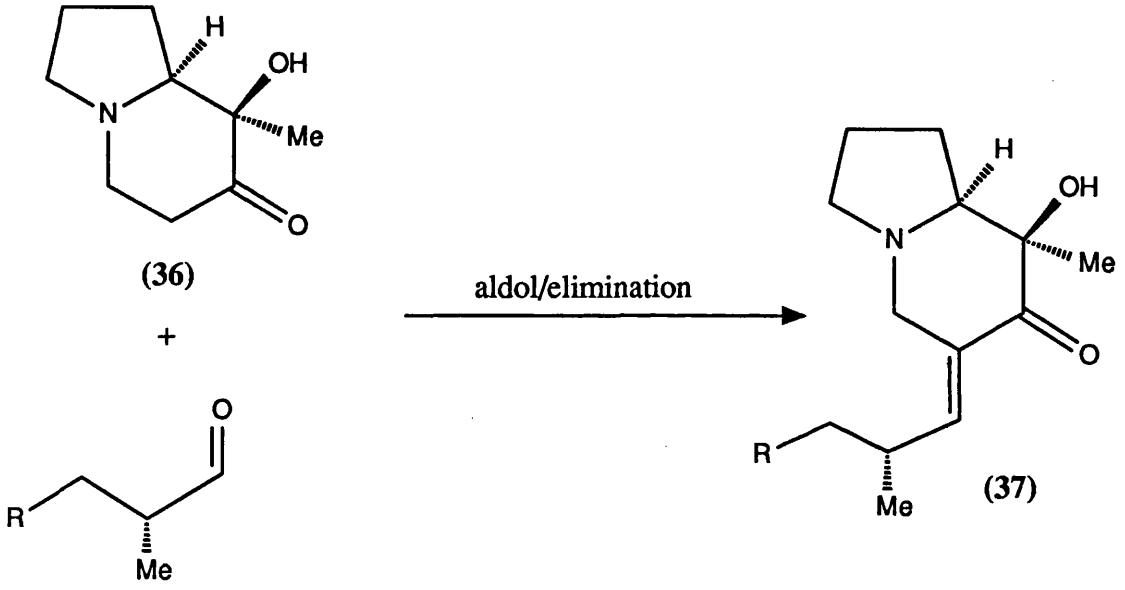

1) Ba(OH)2
2) CH2O, camphorsulphonic acid, NaI, 100°C
H
OH
N
Me
I
OBn
Me
(35)
60%


1) nBuLi, -78°C
2) MeOH
3) Li/NH3
Pumiliotoxin A

Scheme 7

A more recent and highly selective approach to these alkaloids and, in particular, to introduction of the Z-alkylidene subunit, was reported by Overman in an alternative total synthesis of the parent pumiliotoxin A (Scheme 7).[4f]

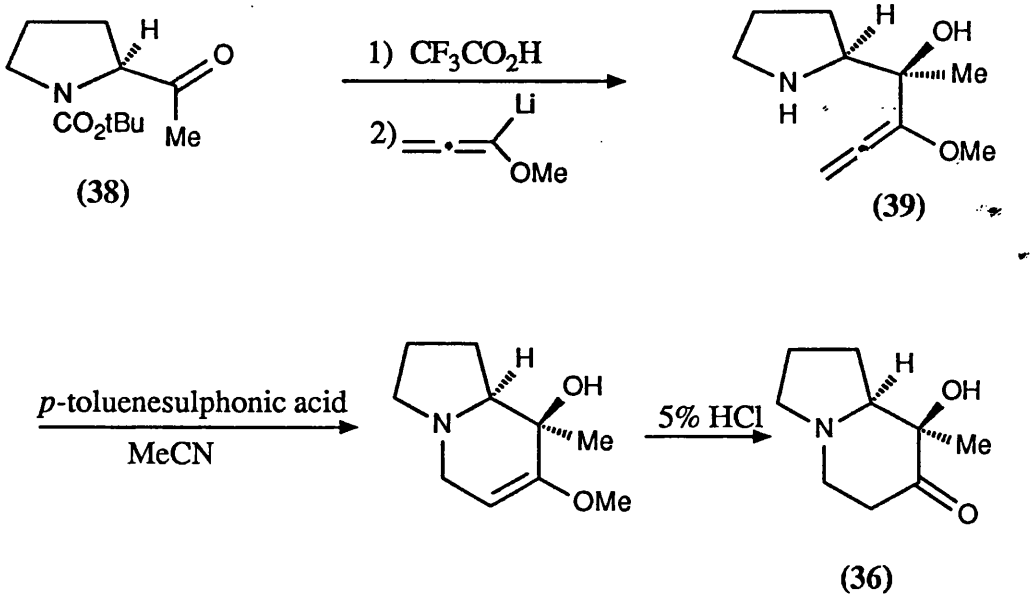
Treatment of the alkynylalane derived from **(33)** with epoxide **(14)** afforded the acetylene **(34)** in high yield. Hydrolysis of the carbamate, followed by iminium ion formation and iodide promoted cyclisation in an antarafacial manner across the acetylene effected conversion to the vinyliodide **(35)** stereospecifically. Reduction and debenzylation concludes an impressive route to (+)-pumiliotoxin A in 43% yield over five steps.



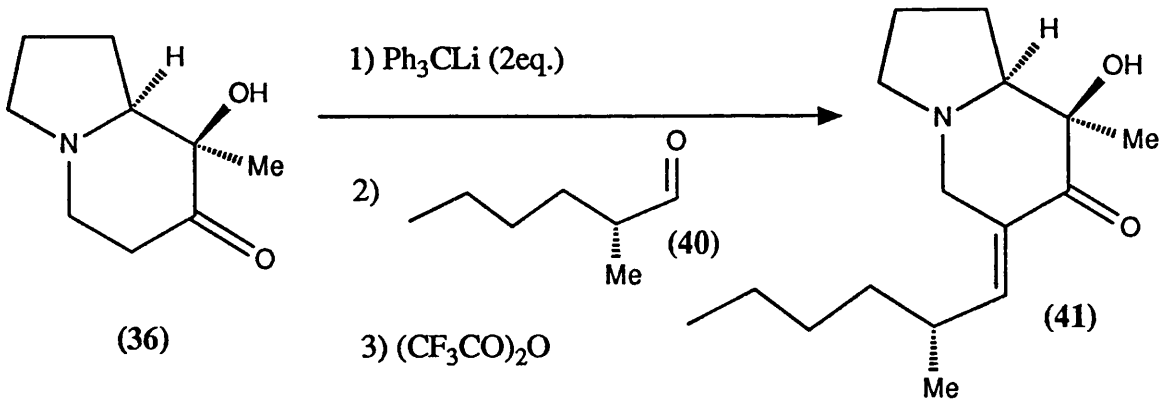
Scheme 8

The allopumiliotoxin subclass of the pumiliotoxin A family has also been the subject of a number of successful synthetic endeavours during recent years. A crucial step in Overman's enantioselective total synthesis of allopumiliotoxins 267A and 339B is shown in general terms in Scheme 8.[4c] The stereochemistry of the alkylidene chain in **(37)** is controlled by an aldol-elimination sequence in which the thermodynamic preference for E-enone is exploited.

The methyl ketone **(38)** is converted to the allenic methyl ether **(39)** as the only detectable isomer (Scheme 9). Cyclisation under mildy acidic conditions and subsequent hydrolysis completes the formation of the indolizidine skeleton **(36)**.

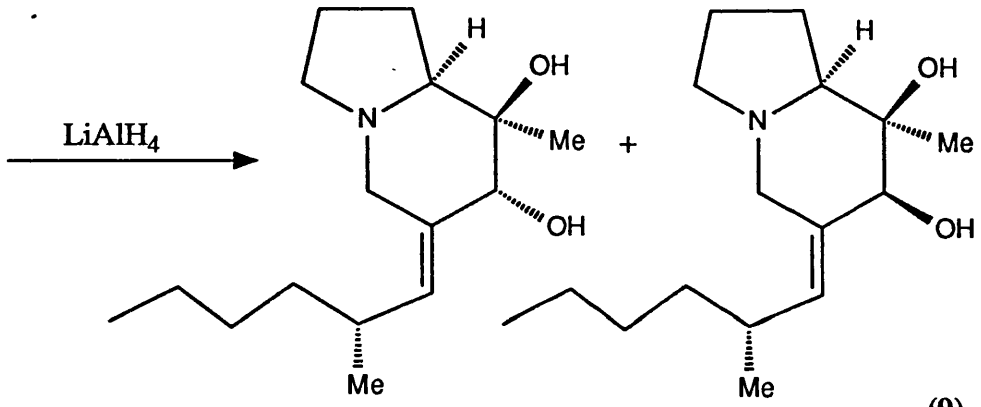


Scheme 9



(36)

(41)



(42)

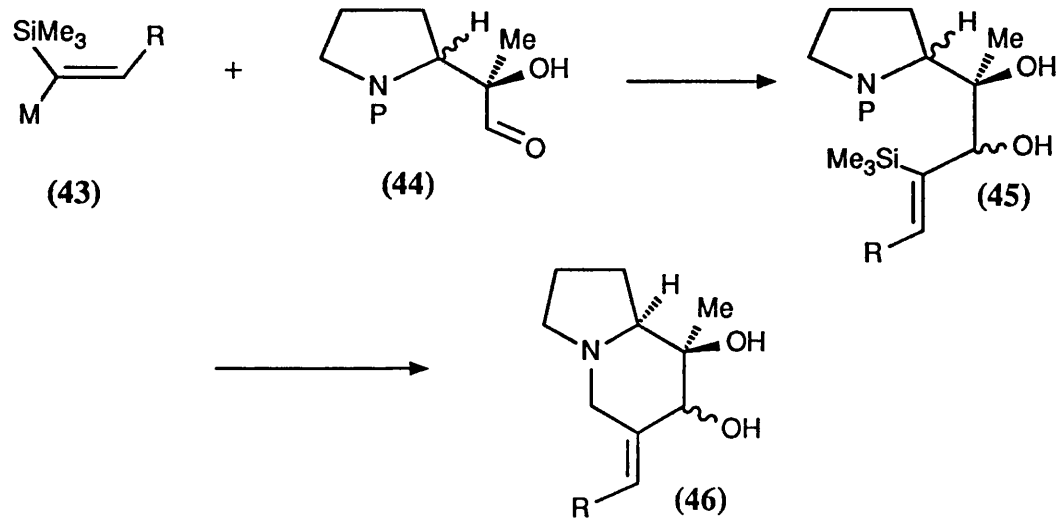
(9)

(+)-Allopumiliotoxin 267A

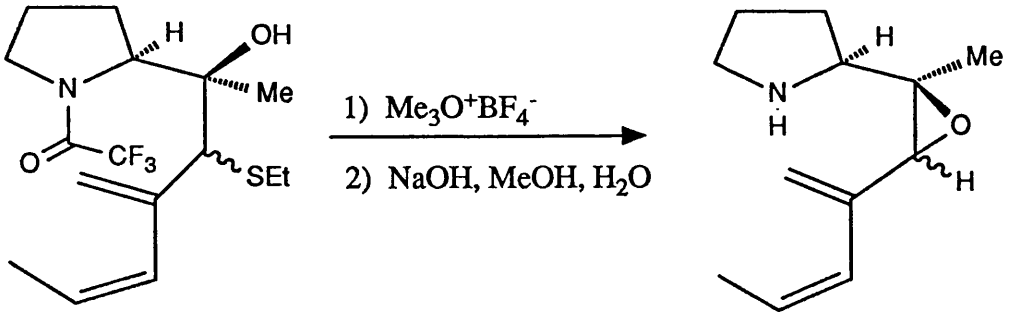
Scheme 10

The corresponding lithium dianion, when combined with the chiral aldehyde (**40**) (Scheme 10) afforded, on dehydration, the E-enone (**41**) as the major product. Stereocontrolled carbonyl reduction remained a problem, however, and the required axial alcohol for (+)-allopumiliotoxin 276A could only be isolated in low yield. The more complex allopumiliotoxin 339B was prepared in a similar manner, employing the appropriately functionalised aldehyde in the aldol elimination sequence. Carbonyl reducton formed once again the alcohol in the equational orientation, this being the required stereochemistry for the more complex alkaloid. The subsequent manipulations of the side-chain were those employed in the total synthesis of pumiliotoxin B described earlier.

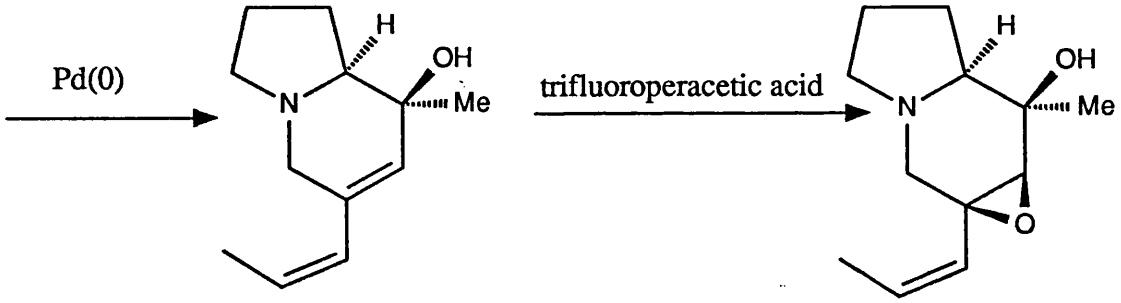
The problem of control of stereochemistry at the C7 allylic hydroxyl group was tackled by Overman in 1988 in a route to the allopumiliotoxin skeleton employing, once again, the vinylsilane-iminium ion methodology.[4g] The strategy is shown in Scheme 11 and involves stereocontrolled attack by a metallated vinylsilane (**43**) on the aldehyde (**44**) to afford the allylic alcohol (**45**). Manipulation as in previous syntheses then completes construction of the azabicyclic system (**46**).



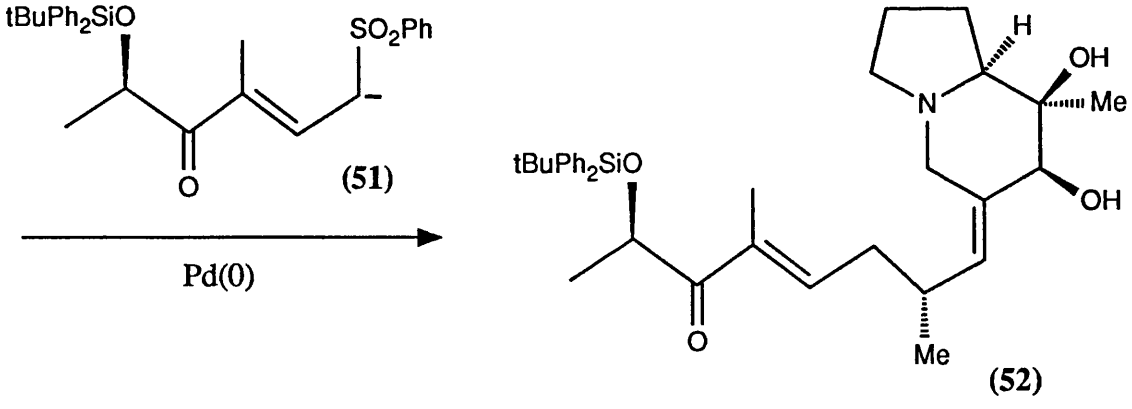
Scheme 11



(47) (48)



(49) (50)



(52)

$LiAlH_4$

Allopumiliotoxin 339B

Scheme 12

In 1989 was seen the first total synthesis of a member of the pumiliotoxin A family from a group other than Overman's. Trost reported the synthesis of allopumiliotoxin 339B in which a key transformation was a highly regio- and stereoselective π-allyl alkylation (Scheme 12).[4h] Formation of the epoxide mixture **(48)** from **(47)** is followed by palladium(0)-mediated opening of the vinyl epoxide functionality to release the tertiary alcohol and to allow cyclisation onto the resultant π-allyl palladium subunit in a 6-endo cyclisation by the pyrrolidine nitrogen, establishing the indolizidine skeleton **(49)**. Hydroxyl directed epoxidation to **(50)** and subsequent π-allyl palladium formation allows highly stereoselective and regioselective alkylation by the sulphone **(51)** to generate the required Z-alkylidene. *Syn*-selective reduction accompanied by desilylation as in Overman's synthesis completes this elegant route to a very complex target.

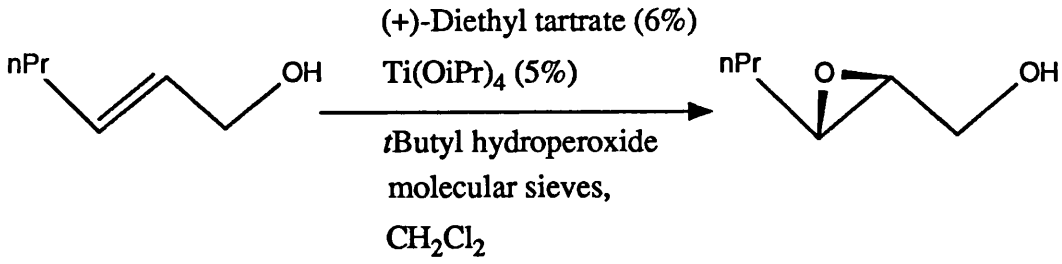
In each of the syntheses described in this section, the (S)-stereochemistry at C8a of the bicyclic framework has been introduced from the beginning of the sequence, in the form of a proline derivative. The synthesis described in this present work tackles the stereochemical problem posed by the stereogenic centre at the ring junction; efforts are made to control this stereochemistry, in an absolute sense, in asymmetric cyclisations of chiral *N*-substituted γ-allenic amines, promoted by metal electrophiles. The remainder of this introduction concentrates on past studies that have been carried out concerning the use of carbon based π-systems in stereochemically controlled interactions and transformations.

1.3 Face Selectivity in Electrophile Activation of Carbon-Based π-systems

1.3(i) The chemical versatility of carbon-carbon double bonds has become an indispensable tool in modern synthetic organic chemistry.[15] Their electron-rich nature enables electrophilic activation to take place and subsequent nucleophilic attack introduces a wide degree of flexibility in terms of functionality of the product. With prochiral double bonds, where at least one terminus is non-symmetrically substituted, reaction leads to the formation of chiral products. In a synthetic climate that demands a high degree of stereocontrol in such transformations, including control of absolute stereochemistry, a number of alternative approaches have been developed to meet this need.

In general terms the source of asymmetry may be the reactant (the electrophilic species) or the substrate incorporating the carbon-based π-system. The first approach, where asymmetry in the product is derived from the reactant, is the basis of a range of well-refined catalytic asymmetric transformations. This review will begin by briefly describing the huge advances made in this field and, more generally, in the area of enantioface selective interaction of chiral electrophiles with prochiral olefins. The review will then focus on the use of chiral substrates incorporating a carbon-based π-system and the investigation of diastereoface selectivities in the interaction of the double bond with electrophiles. In particular, this section will illustrate the importance of anchimeric coordination to direct the electrophile preferentially onto one of the two possible faces of the double bond. Examples will be cited where the diastereoface selectivity has been inferred from the stereochemistry of the reaction products or where isolation of a stable intermediate allows direct determination of the orientation of the interaction.

Since most of these studies have been carried out using alkenes as the reactive π-system, the final section of the discussion will illustrate examples where allenes have been shown to undergo electrophilic activation in a similar manner. Such parallel behaviour augurs well for the potential of these synthetically more versatile π-systems to undergo face selective electrophile-mediated functionalisation.

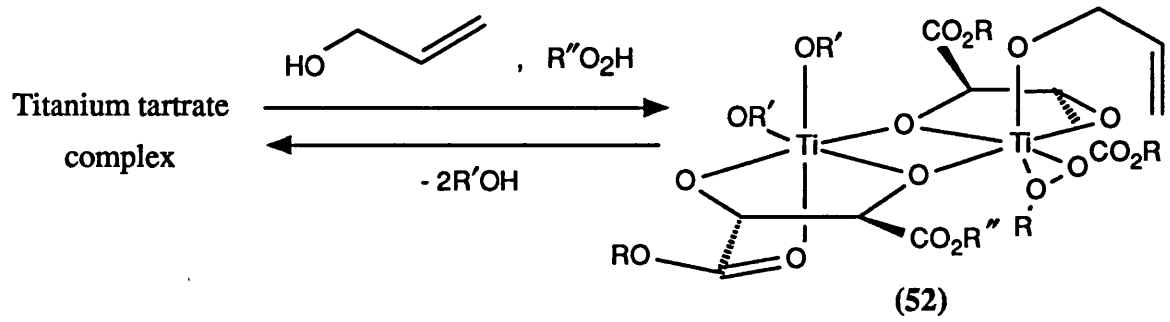

nPr
OH
(+)-Diethyl tartrate (6%)
Ti(OiPr)4 (5%)
tButyl hydroperoxide
molecular sieves,
CH2Cl2
nPr
O
OH

Scheme 13

1.3(ii) Interaction of Prochiral Substrares With Chiral Electrophiles

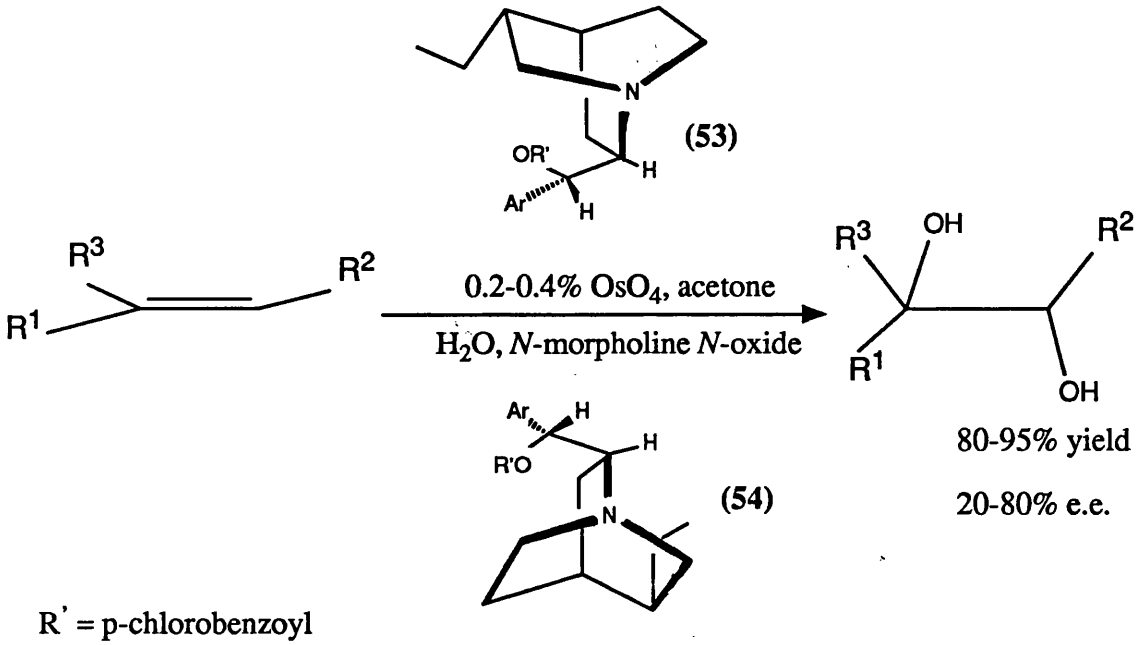
Many reviews have appeared recently, documenting the extraordinary advances made over the last decade in the highly significant area of catalytic asymmetric induction.[16] This section attempts merely to indicate the degree of success that has been achieved in transforming chiral information from an asymmetric metal electrophile to prochiral alkene substrates.

Perhaps the most rigorous test of a novel synthetic transformation, in terms of its efficiency and versatility, is the frequency of its use. The asymmetric epoxidation of prochiral allylic alcohols, developed by Sharpless during the 1980's, would appear to be the most impressive in this respect.[17] The epoxidations are usually carried out with stoichiometric amounts of titanium alkoxides/tartaric acid esters. More recently, however, a truly catalytic system, employing molecular sieves, has been developed.[18] The success of this procedure is indicated in Scheme 13 and has now been adopted as reliable and powerful tool used widely in syntheses carried out by other groups.[19] It is suggested that asymmetric induction results from a reaction pathway proceeding preferentially through one of two possible diastereomeric transition states involving coordination of the hydroxyl function of the substrate to the chiral environment of the dimeric titanium system **(52)** (Scheme 14). That the hydroxyl functionality is necessary for efficient asymmetric epoxidation has been demonstrated by the continued failure to achieve epoxidation of simple olefins using chiral catalysts with product enantiomeric excesses of greater than 50%.[21]



(52)

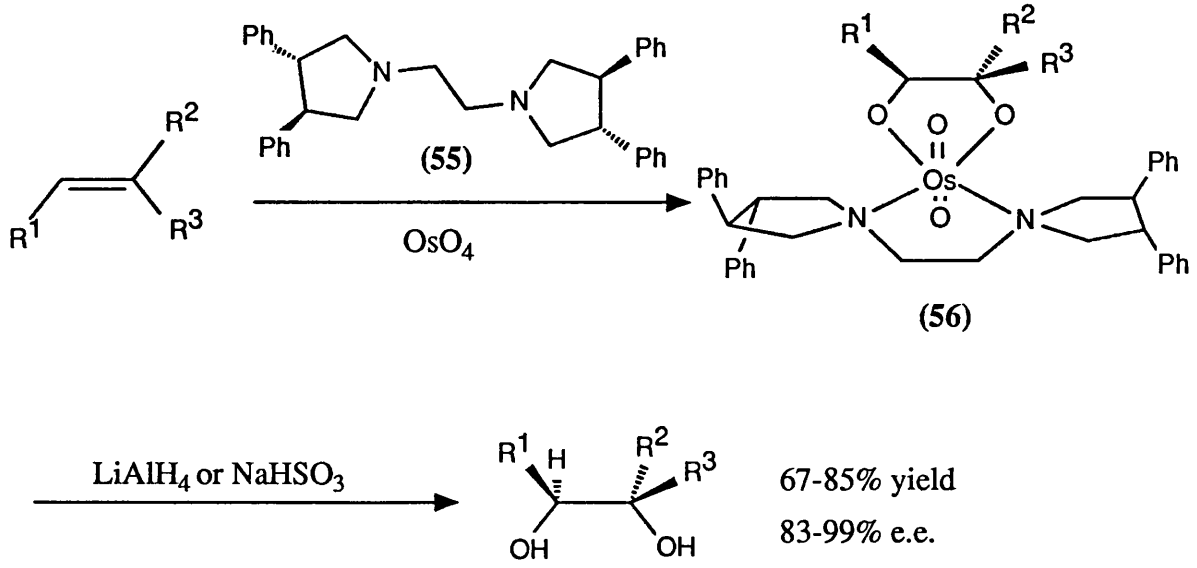
Scheme 14


(53)
0.2-0.4% OsO_4, acetone
H_2O, *N*-morpholine *N*-oxide
(54)
80-95% yield
20-80% e.e.
R' = p-chlorobenzoyl

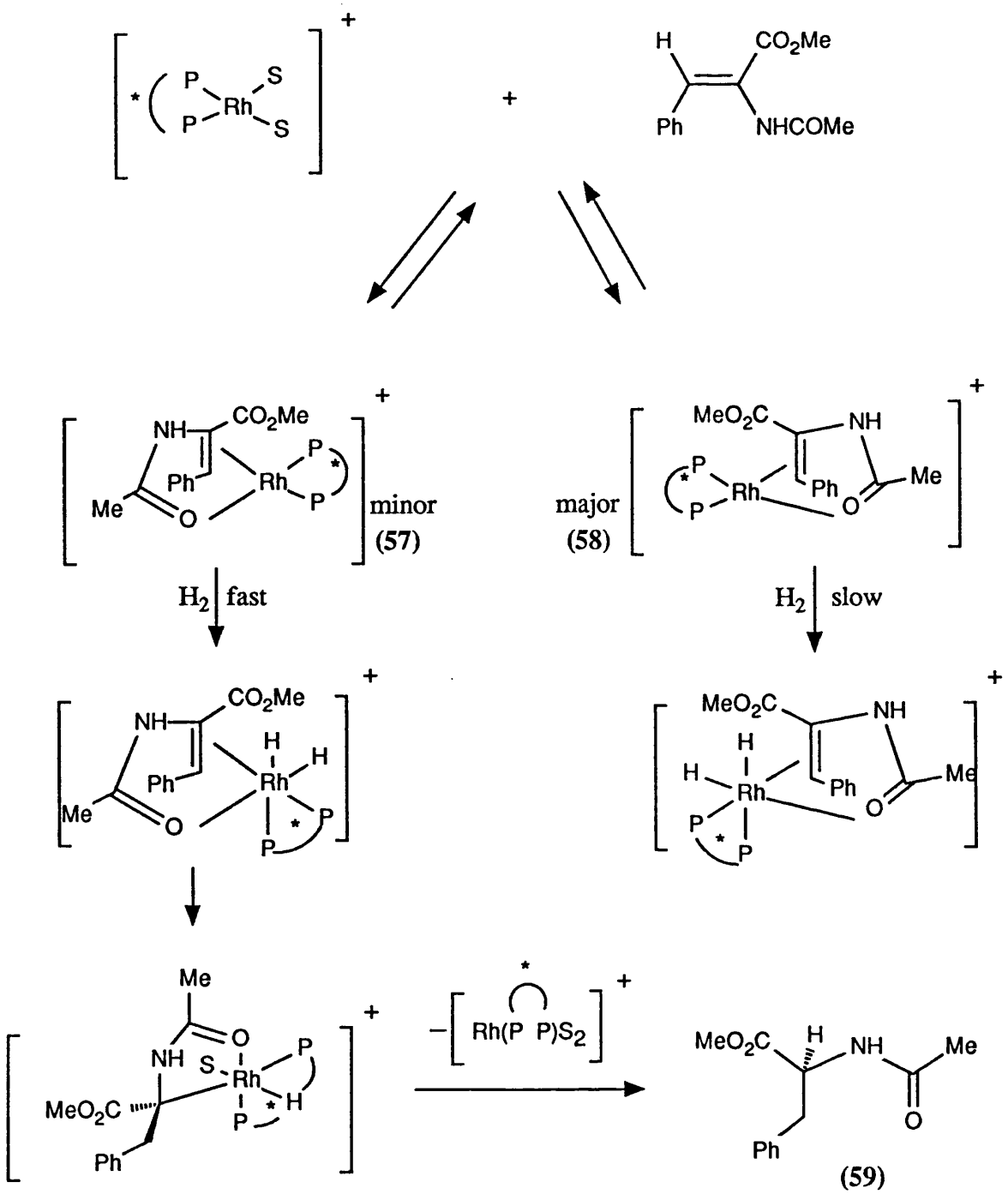
Scheme 15

A related process, developed concurrently by Tomioka[22a], Sharpless[22b] and Corey[22c]is the asymmetric *cis*-dihydroxylation of alkenes by osmium tetroxide, accelerated by chiral ligands. The Sharpless process (Scheme 15) employs catalytic quantities of osmium tetroxide in the presence of cinchona alkaloid derivatives and *N*-methylmorpholine *N*-oxide as a catalyst reoxidant. The sense of face selectivity depends on whether a dihydroquinidine- or a dihydroquinine ester ((**53**)/(**54**)) is used as the chiral ligand.

The system developed by Tomioka employs the D_2 symmetric chiral diamine (**55**) and is shown in general terms in Scheme 16. The observed enantioface differentiation is kinetically controlled by the relative energies of the diastereomeric transition states leading to the intermediate osmate complex (**56**). Corey has also offered a mechanistic rationale involving minimisation of steric repulsions in a [3+2] cycloaddition pathway. This transformation offers greater versatility than the epoxidation process in that there is no requirement for the presence of an allylic hydroxyl functionality to ensure high enantioface selectivity.



Scheme 16



$\overset{*}{\frown}$
P P = chiral diphosphine ligand

S = methanol

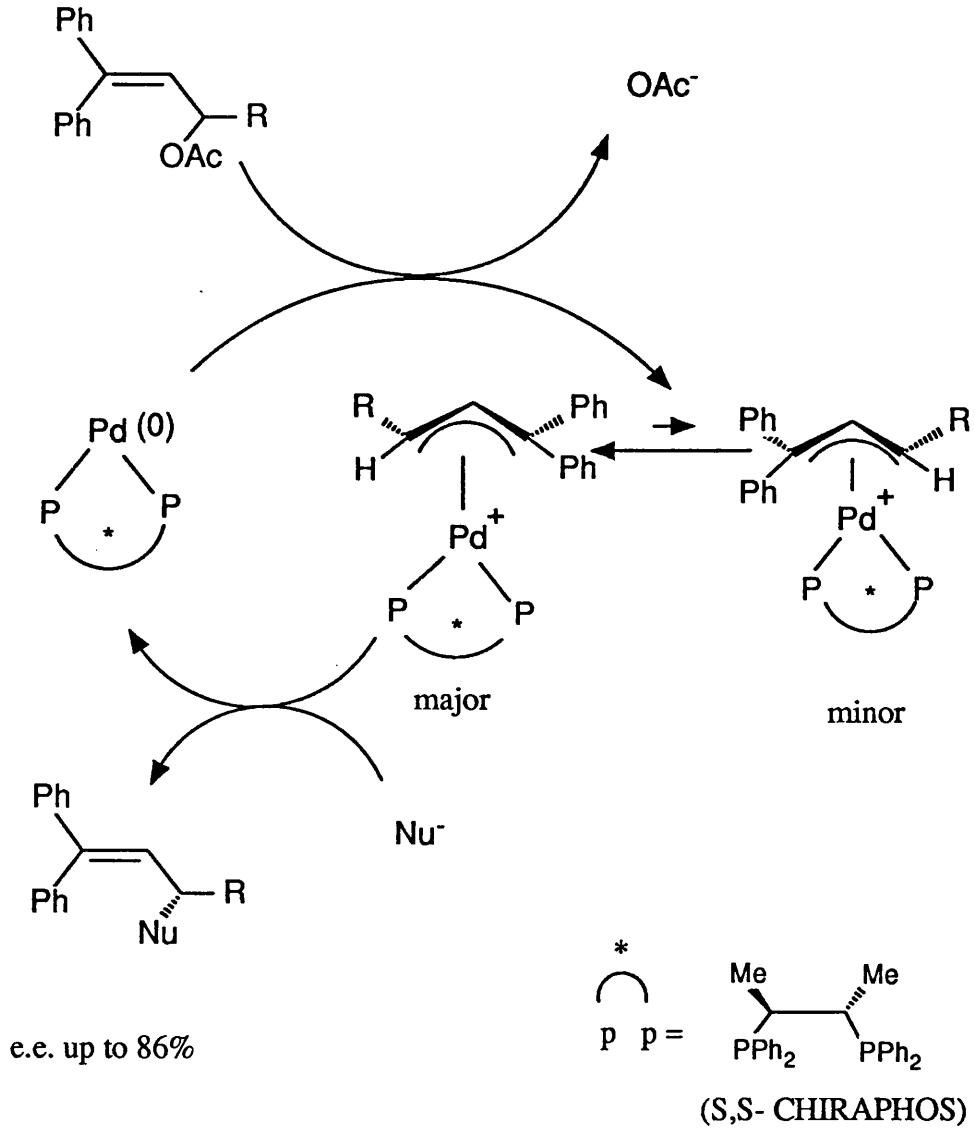
Scheme 17

Another widely used asymmetric catalytic transformation is asymmetric hydrogenation.[23] Like epoxidation, it suffers from the limitation of the need for a coordinating group in the substrate, but is nonetheless an efficient synthetic technique employed on an industrial scale The landmark in this area appeared in 1975 by the Monsanto group with the highly stereoselective reduction of *N*-acetyl dehydroamino acids, catalysed by rhodium complexed to a chiral biphosphine ligand. This constitutes a key step in the synthesis of L-Dopa.[24]

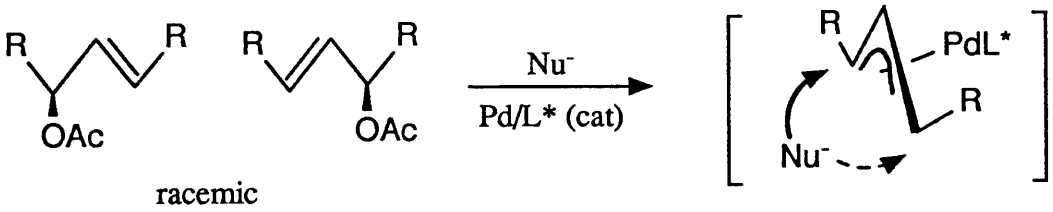
Since then, some of the most impressive results have been achieved by Noyori using ruthenium complexed by the bulky chiral ligand BINAP.[25] A range of alkenes with an adjacent polar group e.g. allylic alcohols, can be hydrogenated with very high stereoselectivity (often >99%ee).

The reaction mechanism of these enantioselective hydrogenations has been elucidated by Halpern.[23b] Bidentate coordination by a combination of the carbon-carbon double bond and the additional ligand present in the substrate results in the formation of two equilibrating diastereomeric intermediates **(57)** and **(58)**. In the case of dehydroamino acid substrates it is found that the minor diastereoisomer **(57)** is the more reactive, leading to more rapid oxidative addition of hydrogen and, on decomplexation, the observed product enantiomer **(59)** is formed (Scheme 17).

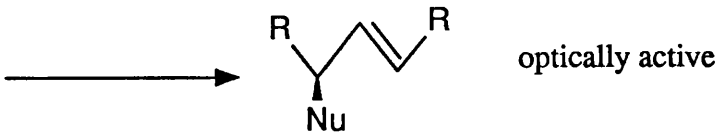
The mechanism of enantioselective hydrogenation contrasts with that of palladium-catalysed asymmetric allylation reactions in which the major product enantiomer is derived from the major diastereoisomer of equilibrating intermediates[26,27] (Scheme 18).



Scheme 18

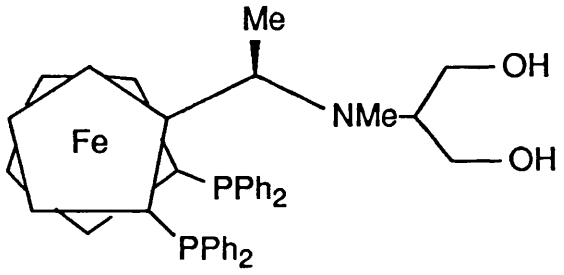


racemic



optically active

L* =



Scheme 19

Hayashi has developed a highly efficient system for palladium-catalysed asymmetric allylation in which optically active ferrocenylphosphines containing a functional group on the side chain resulted in products with up to 92% optical purity (Scheme 19).[28] The *N*-methyl-*N*-bis(hydroxymethyl)methylamino group attached to the ferrocene side chain in the ligand L^* is thought to interact with the carbon-based nucleophile by hydrogen bonding as shown in Figure 2. This interaction would then lead the high stereoselectivity observed, with the nucleophile being delivered preferentially to one of the two termini of the π-allyl system. Similar ferrocenyl ligands have been used by Hayashi and Kumada in Grignard cross-coupling reactions and hydrogenations.[29]

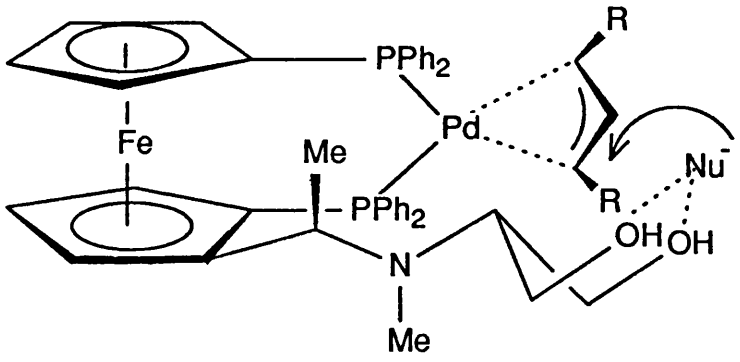
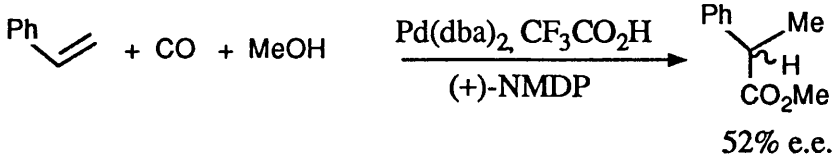
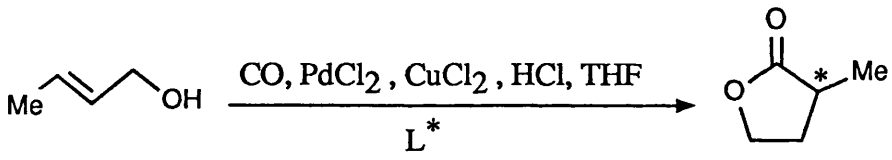


Figure 2



NMDP = neomenthyldiphenylphosphine

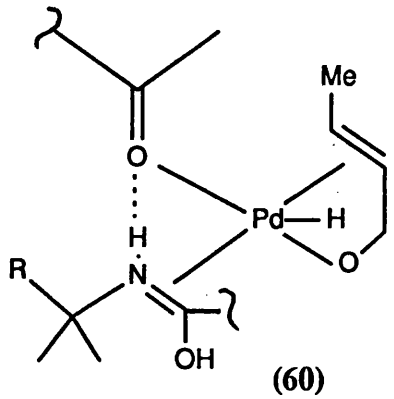
Scheme 20



Scheme 21

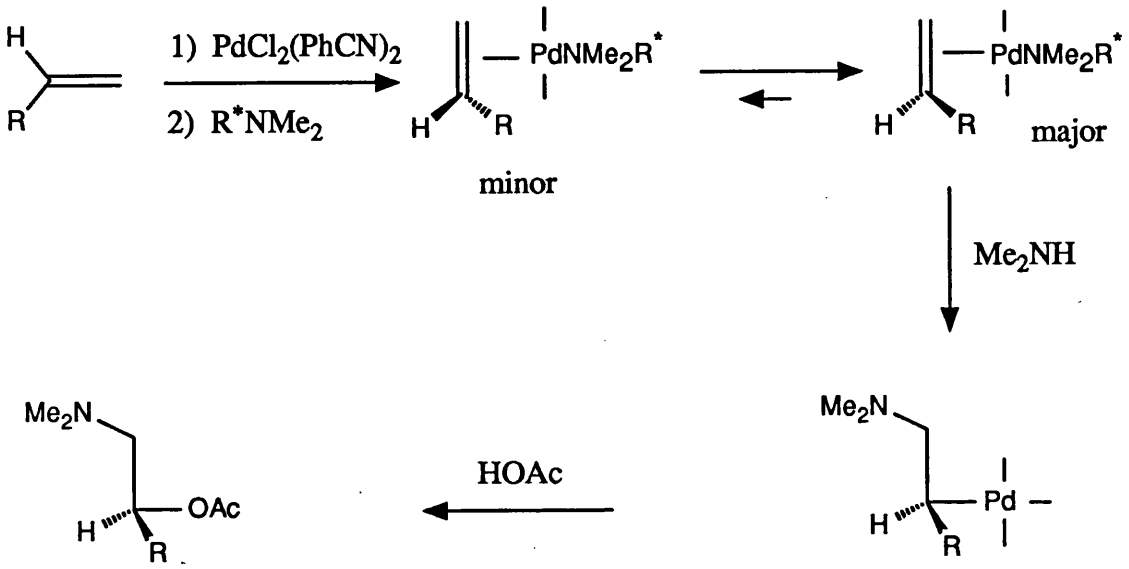
The hydroformylation of olefins has been an industrially important reaction for many decades. Successful approaches to the asymmetric transformation have been developed over the last few years[30,31] and recently Stille[32] reported enantiomeric excesses of up to 95% using platinum catalysts containing chiral phosphine ligands.

Methoxycarbonylation of prochiral olefins is a related process that has received increasing attention. In 1982, the first significant advance in this field was reported using palladium catalysis in the presence of a chiral diphosphine ligand (Scheme 20).[33] More recently, Alper has improved on this enantioselectivity in the palladium catalysed carbonylation of allylic alcohols (Scheme 21).[34] The use of poly-L-leucine, diethyl-L-tartrate and (R)- and (S)-BINAP as chiral ligands is investigated and optical purities of up to 61% ee are obtained. It is proposed that the chiral discrimination step with poly-L-leucine as the source of asymmetry is the intramolecular addition of palladium hydride to the coordinated olefinic substrate in the five-coordinate intermediate palladium complex **(60)** (Figure 3).



(60)

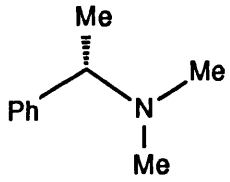
Figure 3



11% e.e.

R = CH_2OPh

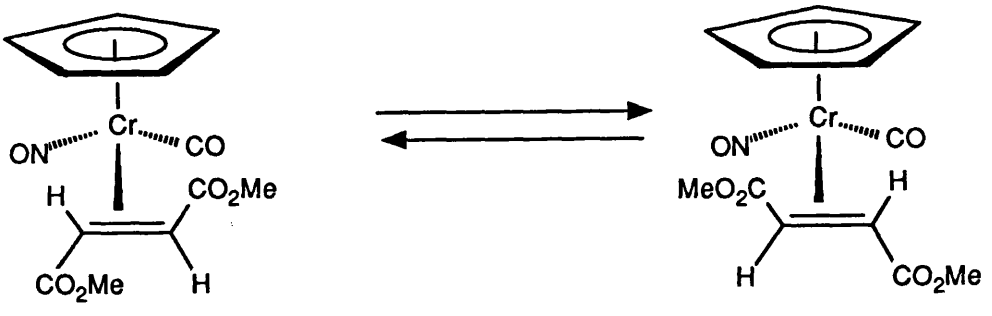
R^*NMe_2 =



Scheme 22

The palladium(II)-promoted asymmetric oxyamination of alkenes reported by Bäckvall in 1982 provides another example of the interaction of prochiral olefins with chiral metal-based electrophiles resulting in the formation of interconvertible diastereomeric intermediates (Scheme 22).[35] Reaction of the intermediate π-complexes with an external amine nucleophile forms enantiomeric products with an optical purity reflecting the ratio of the diastereomeric intermediates at equilibrium. The extent of asymmetric induction in these processes, however, could not be increased much beyond 10% e.e. unless a chiral amine was employed as the nucleophile.

The most challenging field of catalytic asymmetric transformations remains asymmetric carbon-carbon bond formation. The enantioselective catalytic conjugate addition of dialkylzinc reagents to enones, promoted by chiral ligands on Ni(II), provides a highly selective route (enantiomeric excess up to 90%) to optically active β-substituted ketones.[36] No mechanistic interpretation of the role of the norephedrine-derived chiral ligand has been proposed but it would appear that this approach to asymmetric functionalisation of double bonds will have much to offer in future years.



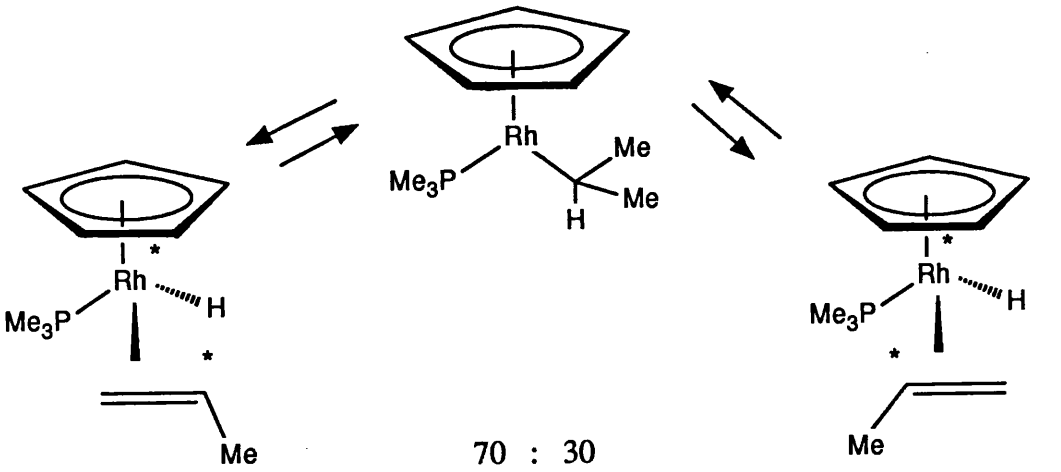
(R-RR) + enantiomer

(R-SS) + enantiomer

Scheme 23

The examples cited so far have not directly studied enantioface selectivity in the interaction of prochiral olefins with chiral electrophiles; such selectivity is inferred from the enantiomeric purity of the products obtained during the overall transformation. Alternative studies have been carried out, however, that monitor the enantioface selectivities of such interactions with stable intermediates. These investigations will be summarised to show how they have provided valuable information concerning the stereochemistry of olefin-metal interactions and are important synthetically for the development of novel asymmetric processes (e.g. polymerisation).

Early studies on the coordination of prochiral olefins to chiral transition metal ions was limited to the investigation of metal complexes that owed their asymmetry to a tetrahedral arrangement of four distinguishable ligands.[37] In 1975, Kreiter[38] reported the thermal behaviour of olefin ligands L in complexes of the type $C_5H_5Cr(CO)(NO)L$. (Scheme 23). Although the major theme of their study was to determine the activation barrier to rotation about the olefin-metal bond, it was recognised that with dimethylfumarate as the coordinating alkene two possible diastereomeric complexes could result and these were observed in ratios between 2:1 and 4:1.



70 : 30

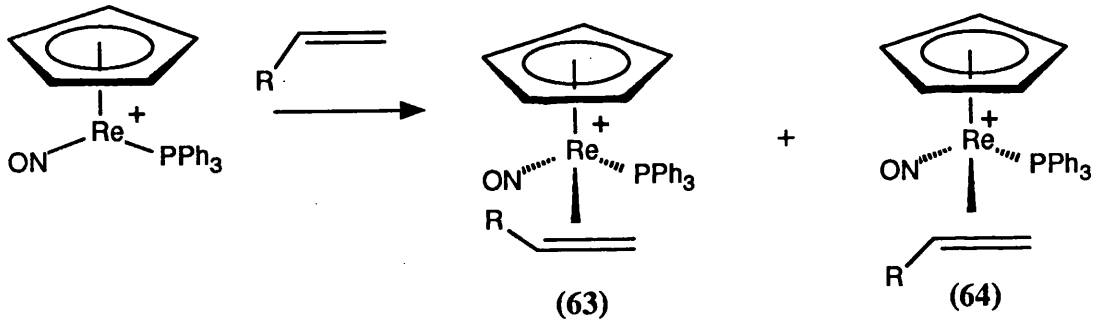
(61)

(R R) + (S S)

(62)

(R S) + (S R)

Scheme 24



(63) **(64)**

kinetic ratio 33 : 67

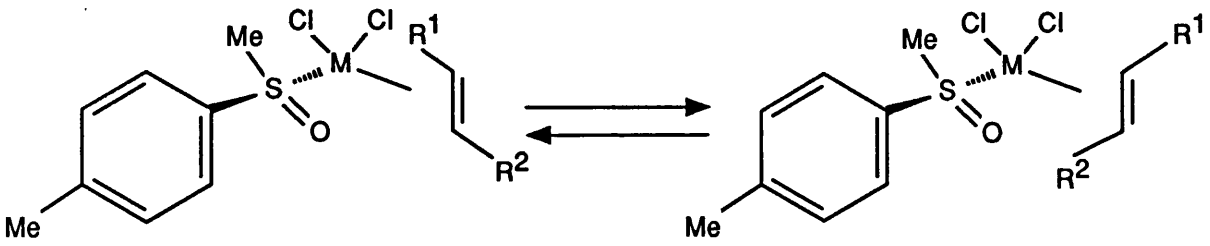
95°C

equilibrium ratio 2 : 98

Scheme 25

It was not until 1982 that the diastereoselectivity of coordination of prochiral olefins in chiral half-sandwich rhodium complexes (Scheme 24) was determined explicitly.[39] Reversible proton transfer allows equilibration of the two diastereomeric complexes **(61)** and **(62)** which, at equilibrium, exist as a 70:30 ratio, reflecting a free energy difference of approximately $2KJmol^{-1}$.

An analogous rhenium-based system was reported a year later by Gladysz [40] in which one diastereoisomer of the chiral styrene complex **(63)** (Scheme 25,R=Ph) underwent complete isomerisation to the diastereomeric complex **(64)** on warming to 95°C. Each diastereoisomer comprises a number of rotamers corresponding to rotation about the olefin-metal bond. A typical range of values for the activation barrier in such isomerism is between 32 and 52 $kJmol^{-1}$ and, as a result, interconversion is usually rapid at room temperature. In many related systems, however, NMR experiments at low temperature have revealed the presence of distinct rotamer populations.[37] Gladysz has rationalised the high thermodynamic enantioface selectivity observed in terms of stereoelectronic considerations in which the alkene conformation that combines maximum overlap of π^* orbitals and the metal complex HOMO with minimisation of steric repulsion is the predominant one.

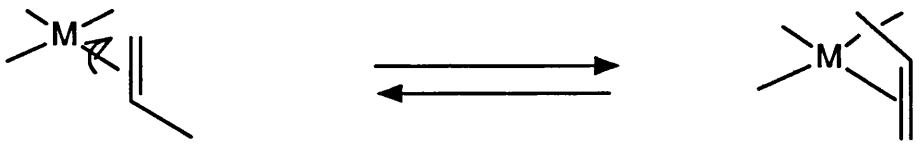


R^1=Ph, R^2=H } diastereomeric ratio = 3:1

R^1=R^2=Me diastereomeric ratio = 2:1

R^1=tBu, R^2=H } single diastereoisomer

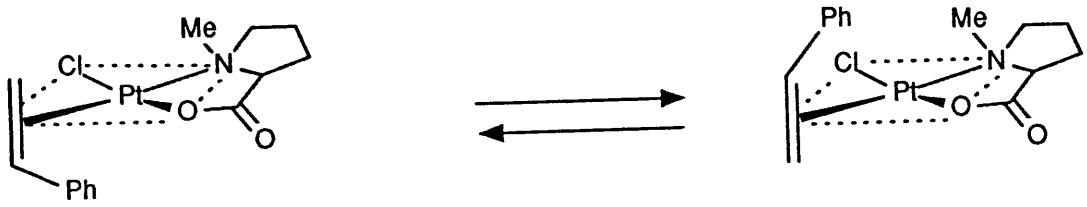
Scheme 26



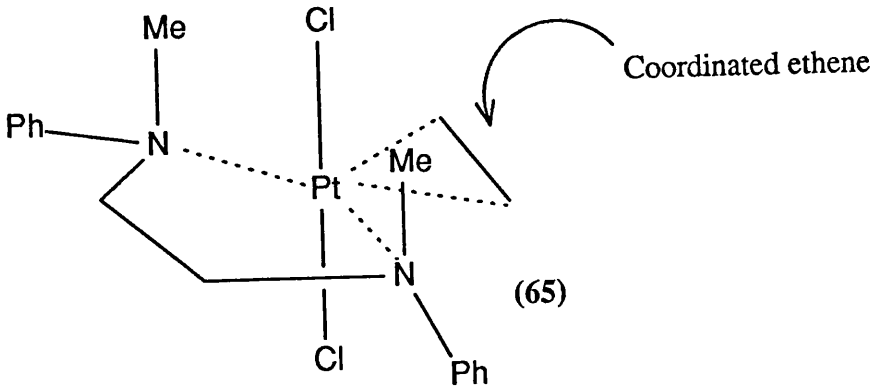
Scheme 27

Towards the end of the 1970's the emphasis began to switch to the preparation of olefin-metal complexes where asymmetry associated with the electrophile was derived from chiral coordinating ligands. Bosnich was the first to carry out a systematic study of the enantioface selectivity of coordination of prochiral olefins to a chiral sulphoxide-platinum(II) species and how this selectivity varied with alkene structure (Scheme 26).[41] The equilibrium involving diastereoisomer interconversion was established rapidly at room temperature. The rate of equilibration was additionally shown to increase with concentration, which led to the proposal that a dimeric species might be responsible for this process. Once again, rotameric interconversion (Scheme 27) was rapid at 31°C and a time-averaged NMR spectrum was recorded for each diastereoisomer.

It is suggested that the freedom of the sulphoxide ligand to rotate about the metal-sulphur bond leads to the only modest levels of diastereoselectivity obtained. Similar reasoning could apply to a rotating olefin ligand although it is argued that the preferred rotamer population is likely to be that in which the orientation of the olefin is perpendicular to the plane defined by the other coordinating ligands. The complex formed with *t*-butylethylene indicates the presence of just one isomer but it is believed that this is not a reflection of the equilibrium situation, rather that it is a kinetic effect.



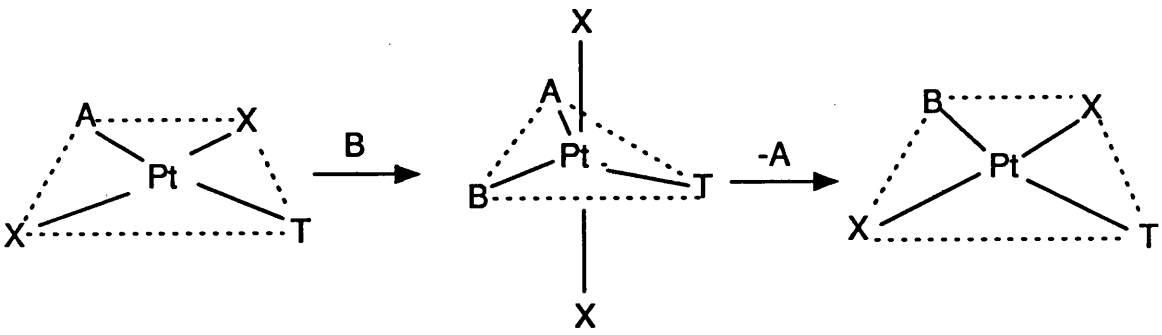
Scheme 28



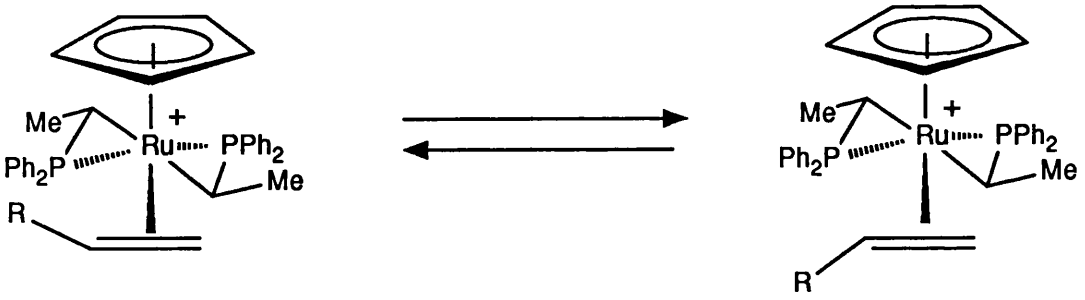
(65)

Figure 4

Following an initial report[42] in 1966 on the stereochemistry of coordination of prochiral olefins to square planar platinum complexes of the type *cis*-dichloro (olefin)(S)-(α-methylbenzylamine) in which observable face-selectivity resulted, Saito[43] published a rather more rigorous investigation in a related system (Scheme 28). Observation of the proton, ^{13}C and ^{195}Pt NMR spectra of diastereomeric platinum (II) complexes of prochiral olefins with *N*-methylproline as a chiral bidentate ligand indicated diastereomeric ratios of up to 1.8:1. The rotamers in Scheme 28 are those in which the phenyl group is pointing towards the smaller *cis*-ligand atom (O). The diastereoisomers undergo rapid and spontaneous equilibration and the more abundant isomers have NMR spectra indicating a higher thermodynamic stability resulting from more efficient donation of electrons from the olefin π-orbital to the platinum σ-orbital. De Renzi has carried out studies using chiral bidentate diamine ligands in five-coordinate platinum complexes.[44] The structure of the complex **(65)** as determined by X-ray analysis is shown in Figure 4 with the ligands around the metal adopting a trigonal bipyramidal geometry and the chlorine atoms occupying the axial sites. It is noticeable that in this five-coordinate species, the olefin lies in the equatorial plane rather than perpendicular. NMR studies indicate a diastereoselectivity of 4:1 when the coordinating olefin is propene and the complexation of fumarodinitrile and acrolein appears to be completely stereoselective in that only one isomeric species is observed in the proton spectrum.



Scheme 29

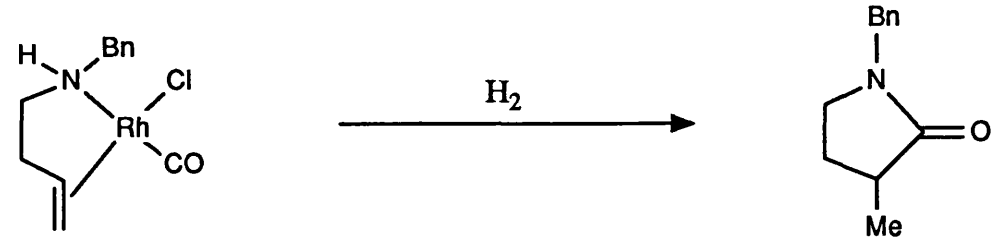


Scheme 30

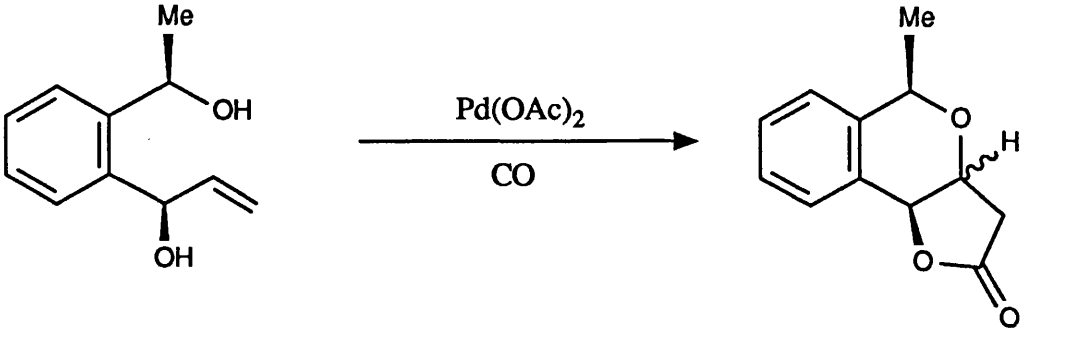
The relevance of this work to square planar complexes was borne out two years later when it was suggested that ligand substitution in square planar four-coordinate *trans*-[PtX_2AT] complexes occur *via* five coordinate intermediates that have trigonal bipyramidal structure (Scheme 29).[45] The degree of diastereotopic discrimination depends strongly on the configuration of the metal centre and coligands and so is different in each of these intermediates.

A significant series of experiments was carried out by Consiglio in 1986 on pseudotetrahedral half-sandwich ruthenium complexes chelated by a chiral biphosphine ligand (CHIRAPHOS) and coordinated by a prochiral olefin (Scheme 30).[46] Equilibration diastereomeric ratios were determined by proton NMR and were shown to vary from 55:45 for methyl acrylate to 95:5 for styrene. The conclusions drawn from this detailed study included the proposal that enantioface selection is influenced by both steric and electronic factors. The presence of the carbonyl group in methyl acrylate resulted in low enantioface selectivity and it is believed that this is the consequence of interaction of the carbonyl oxygen with other ligands in the complex, so as to reduce the differences in the complexation energy of the two enantiofaces. As in previous studies, epimerisation of the complexes is relatively facile at room temperature and is believed to occur by a dissociative mechanism, as might be expected with these coordinatively saturated complexes. The influence on the stereochemistry of coordination by the presence of oxygen atoms has been reported both prior to and following from the findings of Consiglio.[47,48]

The efficiency and potential of catalytic asymmetric allylation reactions has already been discussed.[26-28] The success in this area has initiated interest in isolating and characterising stable, chiral π-allyl-metal intermediates. Following directly from the work of Bosnich, Farrar was successful in obtaining the crystal structure of the major diastereomeric π-allyl palladium complex proposed in the catalytic cycle.[49] Brown has also carried out studies using an alternative chiral biphosphine ligand (DIOP) to chelate stable intermediate π-allyl platinum species.[50] As proposed by Bosnich, the diastereomeric complexes are deemed to undergo interconversion *via* a π-σ-π isomerisation mechanism, promoted by the addition of triphenylphosphine.

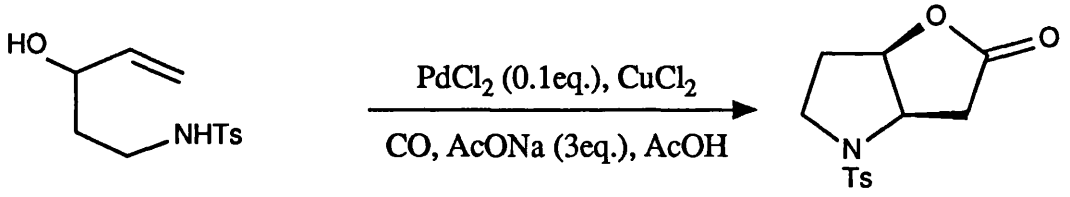


Scheme 31



cis : trans ring fusion (5:1)

Scheme 32



90%

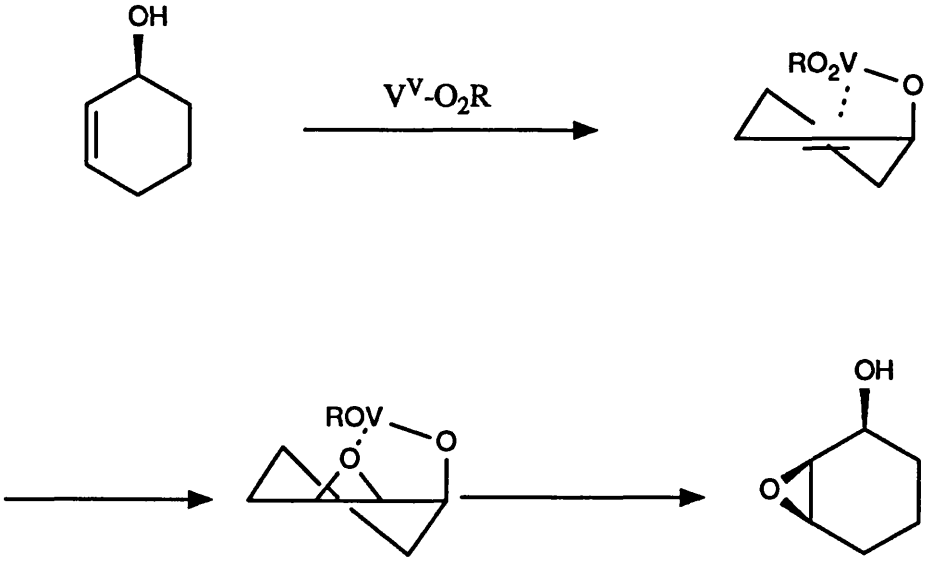
Scheme 33

1.3(iii) Interaction of Chiral Substrates with Achiral Electrophiles

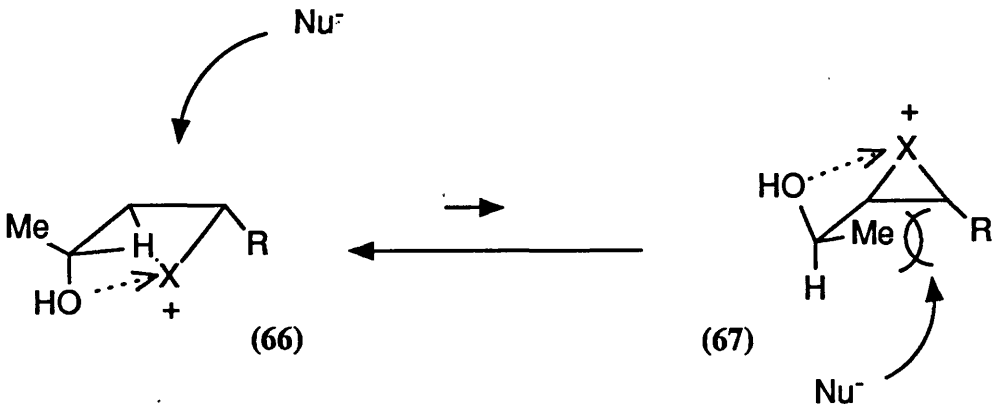
The discussion turns now to the use of pre-existing asymmetric centres present in the reaction substrate to influence the diastereoselectivity of interaction of the olefin subunit with electrophilic species. It will be noted that, in many cases, an additional coordinating group often directly attached to the stereogenic centre is necessary for significant levels of relative stereochemical control to be achieved. The importance of such anchimeric interaction to encourage complex formation or to control regioselectivity in subsequent transformation for achiral substrates has been documented.[51] In the most recent of these examples[51e,51f] (Scheme 31) the regiochemical outcome of hydrocarbonylation reactions of homoallylic amines is directed by coordination of the amine nitrogen to the rhodium complex. In some cases reaction intermediates have been isolated and characterised by X-ray crystallography and clearly indicate coordination of this nature.

Numerous studies have been concerned with stereocontrolled interactions of chiral allylic alcohols and subsequent reactions to form products with a high degree of diastereoselectivity (Schemes 32-34). Scheme 32 illustrates an intramolecular palladium(II)-mediated alkoxycarbonylation/lactonisation that proceeds with a moderate level of diastereoselectivity.[52] This diastereoselectivity is lost when the allylic alcohol portion is *O*-methylated prior to cyclisation, suggesting a strong directing effect of this hydroxyl group favouring a *cis*-fused product. A related system has been developed by Yoshida (Scheme 33),[53] once again the high *cis*-selectivity being attributed to the allylic hydroxyl functionality.

High diastereoselectivities have also been achieved in transformations other than cyclisation processes and the hydroxyl-directed epoxidation of allylic alcohols reported by Sharpless (Scheme 34) is an example of the high degree of control that may be achieved.[54]



Scheme 34



Intermolecular nucleophilic attack - late transition state

OH in-plane

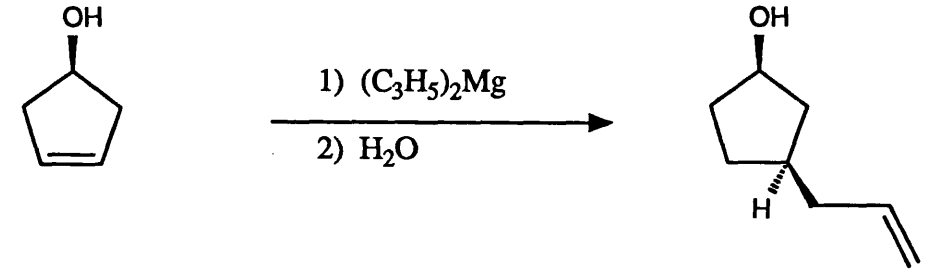
H in-plane

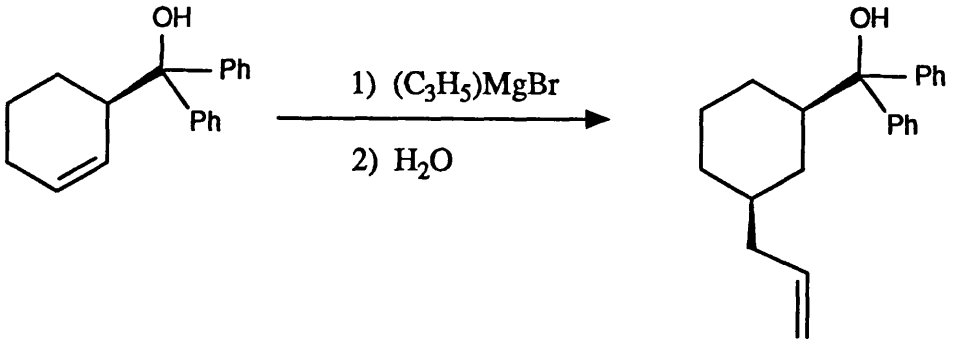
Intramolecular nucleophilic attack - early transition state

Scheme 35

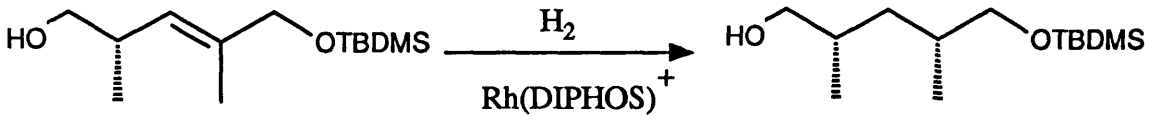
The influence of an allylic functionality on the face selectivity of interaction between a double bond and electrophile has been the subject of a series of theoretical investigations.[55] A distinction is made between intermolecular attack of a nucleophile onto an activated π-bond and intramolecular nucleophilic attack (i.e. cyclisation) (Scheme 35). The former is considered to have a late transition state possessing onium ion-like character. The relative energies of the two possible diastereomeric transition states **(66)** and **(67)** are determined by steric considerations on the basis that the positive charge associated with X is stabilised by interaction with the lone pair of electrons on the hydroxyl functionality. In cyclisation processes, the transition state is deemed to be earlier and possess π-complex character. The face selectivity is determined by least hindered approach of the electrophile E^+ to the more reactive of the two conformers **(68)** and **(69)**.

The directing potential of hydroxyl groups for a wide range of chemical transformations has been recognised for a number of years; a variety of reviews have appeared on the subjects of directed carbometallations[56] and directed hydrogenations.[57] Eisch has shown (Scheme 36) that allylation with magnesium-based reagents proceeds in a *syn*-selective manner relative to the homoallylic hydroxyl functionality.[58,59]

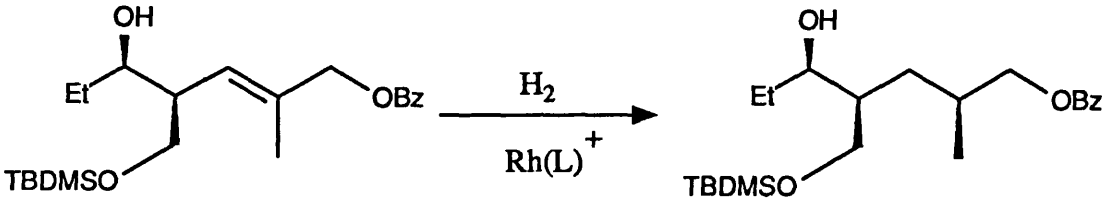




Scheme 36



95:5



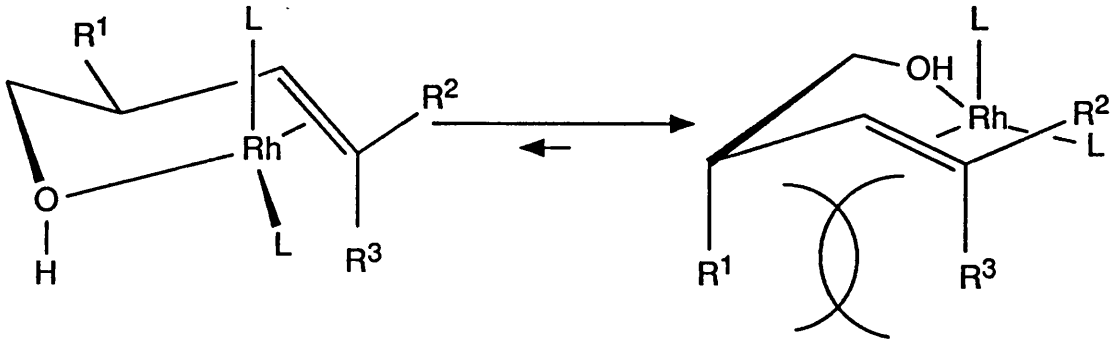
L = DIPHOS 89:1

(+) BINAP 97:3

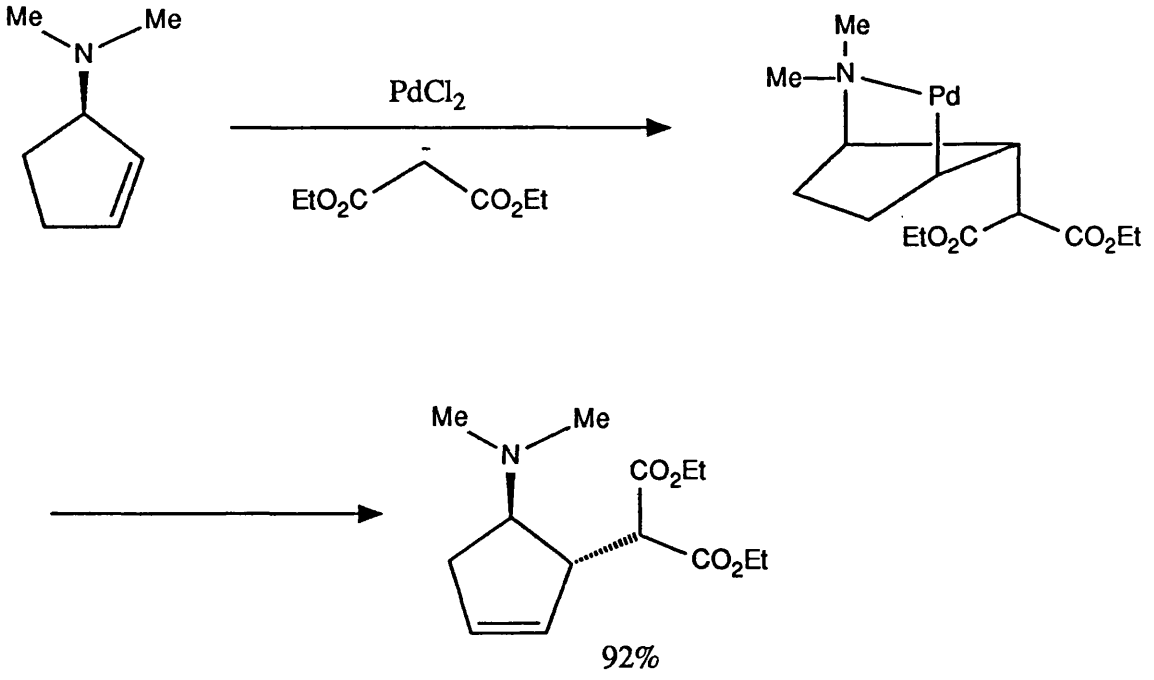
(-) BINAP 92:8

Scheme 37

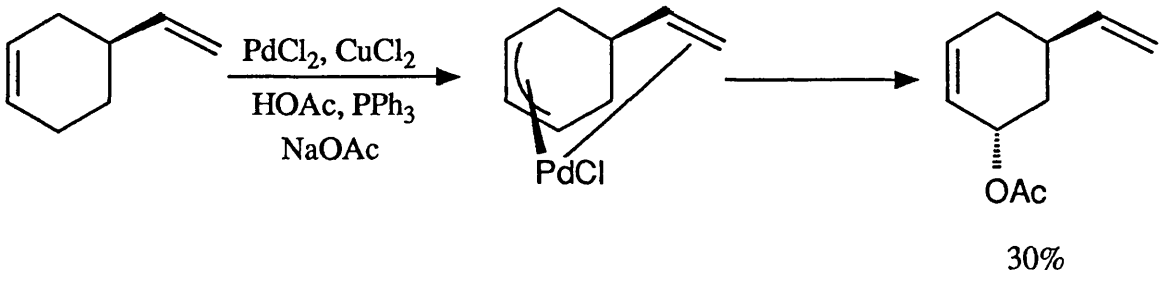
Evans has demonstrated that the stereochemical course of hydrogenation can be controlled by allylic substitution (Scheme 37).[60] The equilibrium depicted in Scheme 38 indicates that coordination by the homoallylic hydroxyl functionality to the rhodium catalyst restricts approach of the reducing species to only one of the two possible faces of the olefin, in order to minimise A(1,3) repulsion.



Scheme 38

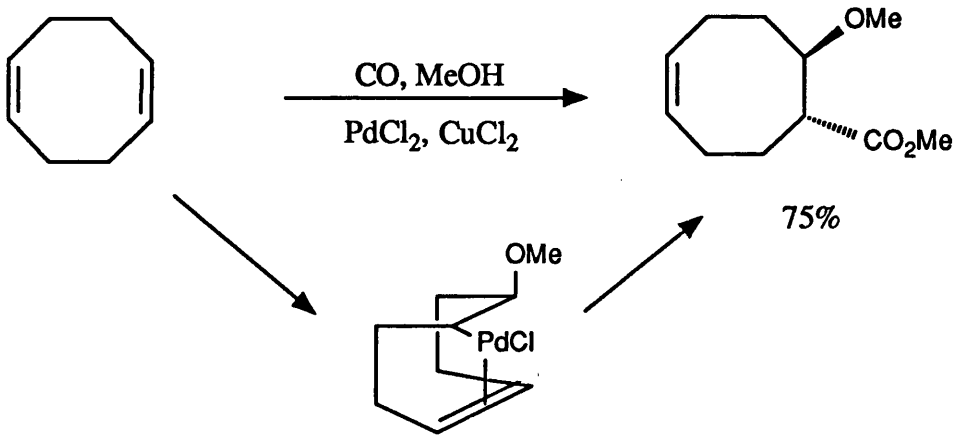


Scheme 39

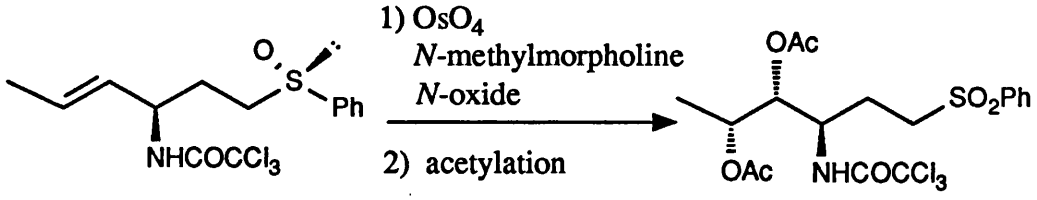


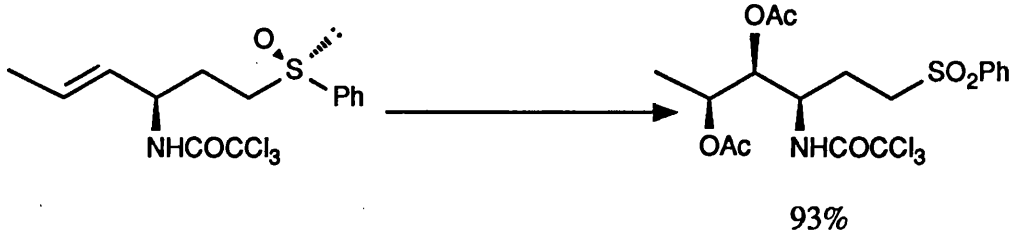
Scheme 40

Functional groups other than hydroxyl have been successful in directing the orientation of approach of a metal to an olefin face : amines (Scheme 39)[61], alkenes (Scheme 40)[62], (Scheme 41)[63] and sulphoxides (Scheme 42)[64] have been shown to be particularly successful in this respect. This last example is especially impressive since the acyclic stereocontrol element is more remote than homoallylic.



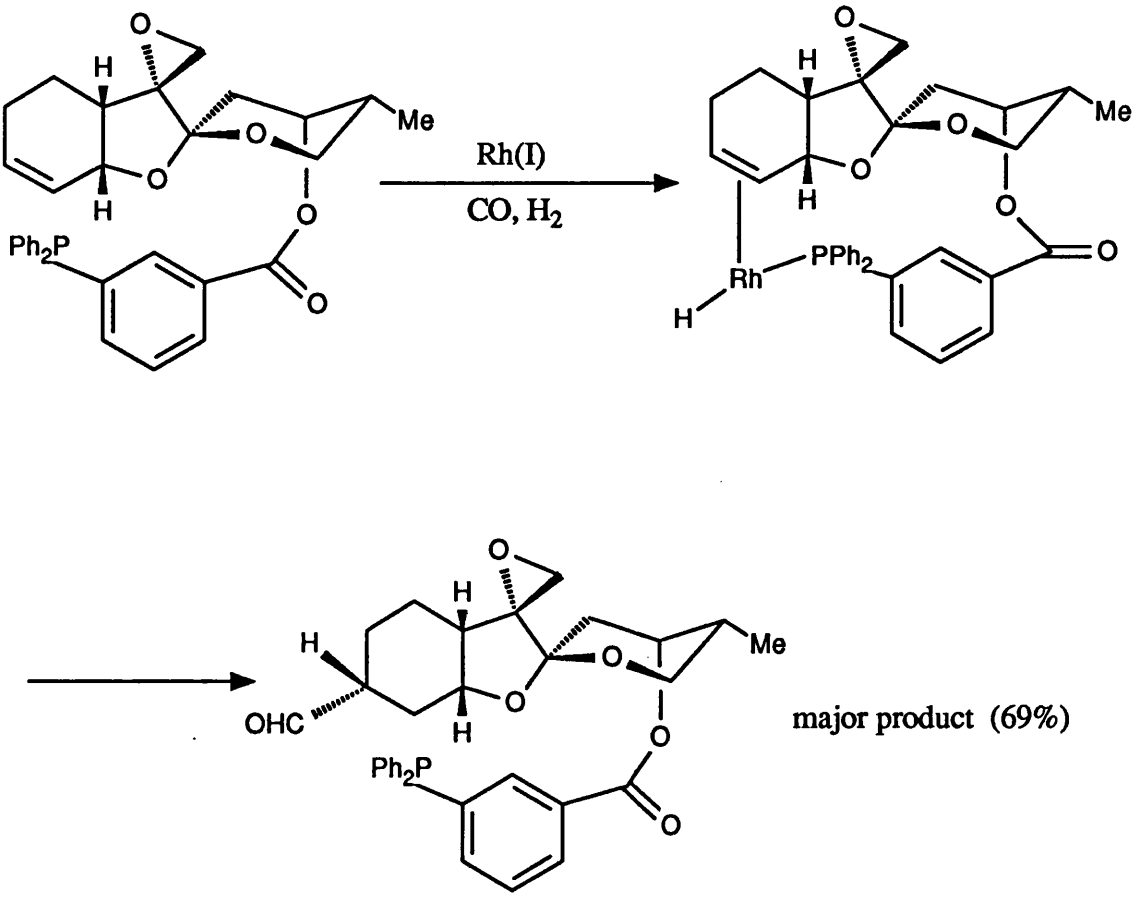
Scheme 41





Scheme 42

This work was followed, two years later, by an elegant example[65] of regio- and diastereoface control in a system conceptually related to those used by Breslow[66] to effect remote functionalisation of steroids (Scheme 43).



Scheme 43

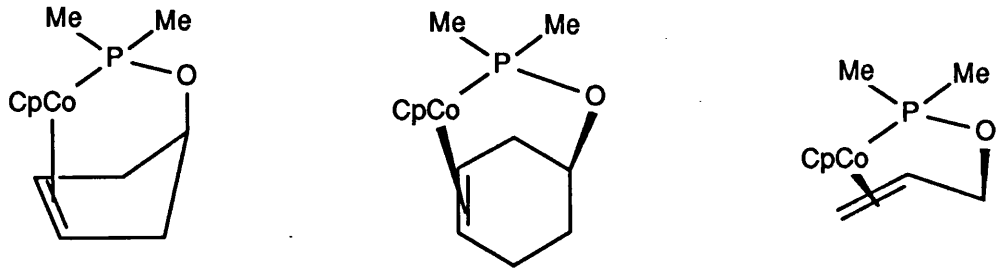
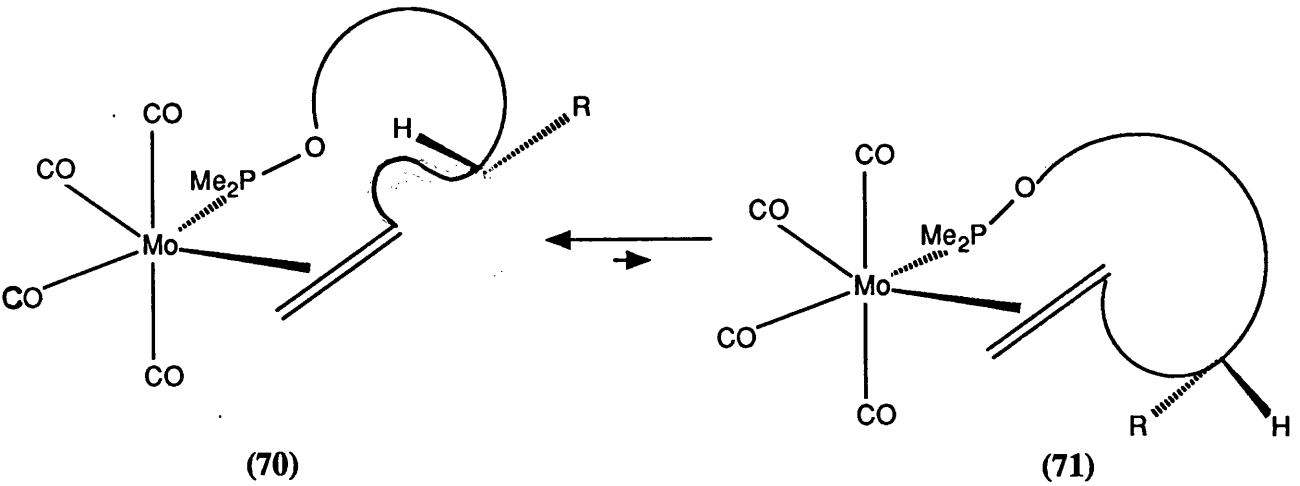


Figure 5

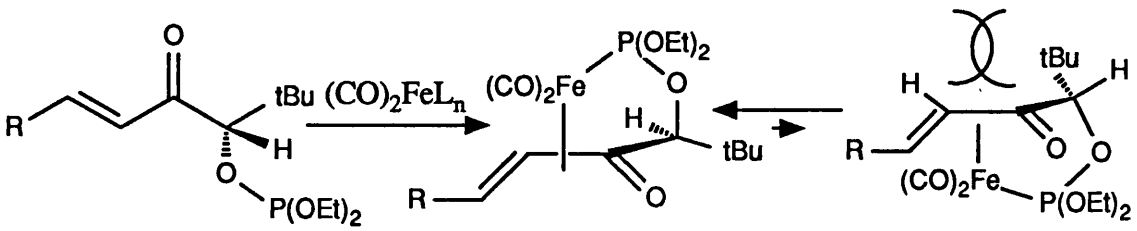


(70) **(71)**

Scheme 44

As a result of the preparation by Collum [67] of unsaturated phosphinate chelates shown in Figure 5, the same group has, more recently[68], carried out a systematic study of diastereoface selectivities of coordination using chiral phosphinate esters (Scheme 44). Selectivities of up to 30:1 were obtained and crystal structures confirmed the proposal that a prerequisite for diastereofacial coordination selectivity was a large preference for the olefin to allign parallel to the P-Mo-CO axis. The preference for **(70)** over **(71)** then results from the least hindered *exo* orientation of the substituent R at the pre-existing stereogenic centre.

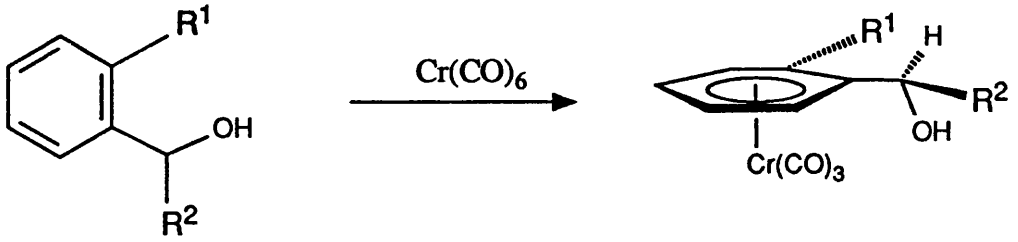
Closely akin to the work of Collum is the recent report by Helquist concerning the highly diastereoface selective chelation of a phosphite-containing α,β-unsaturated ketone system to the $Fe(CO)_2$ group (Scheme 45).[69] The equilibrium between **(72)** and **(73)** shows a marked preference for the former and this is, once again, due to minimisation of steric repulsions, in this case associated with the *t*-butyl group. The structures of the complexes obtained have been determined by X-ray diffraction and monitored by proton NMR which indicated complete diasteroface selection in coordination. This efficient generation of diastereomerically pure enone complexes has a potential use in highly stereoselective transformations. In particular, conjugate additions to these systems have been shown to result in products with enantiomeric excesses of greater than 99%.



(72) **(73)**

Scheme 45

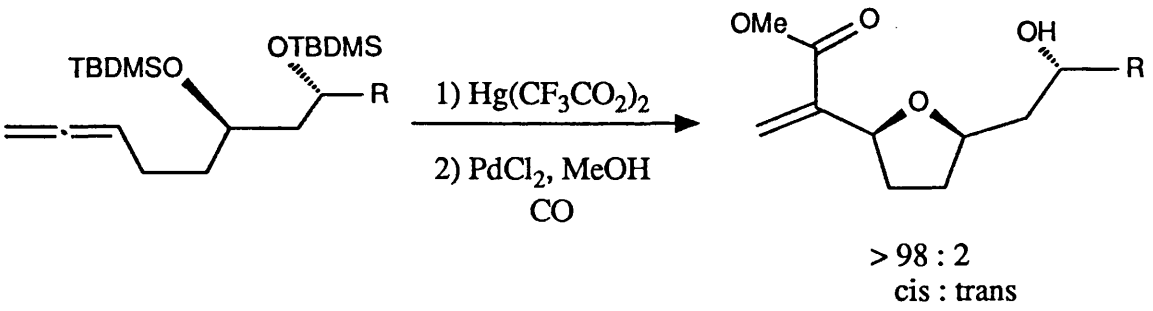
A number of other investigations into the diastereoselectivity of coordination of π-systems incorporated in chiral molecules to metal electrophiles have been carried out, in which the selectivity is determined directly and not deduced from the products of subsequent reaction (Scheme 46).[70]



38 - 86% d.e.

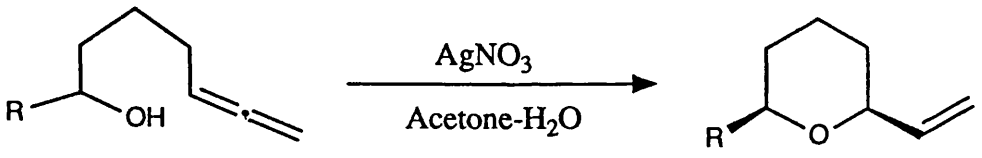
Scheme 46

The coordination of (S)-3-methyl-1-pentene to square planar platinum complexes[71] and trigonal bipyramidal platinum complexes[72] has been studied as models for Ziegler-Natta catalytic sites. These reports indicated highly selective initial coordination followed by rapid equilibration in solution.



> 98 : 2
cis : trans

Scheme 47



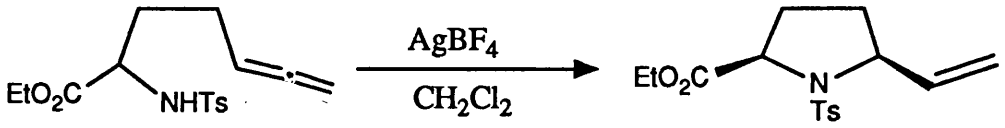
R = Me cis : trans = 71 : 3

Scheme 48

3.1(iv) Interaction of Allenes with Electrophiles

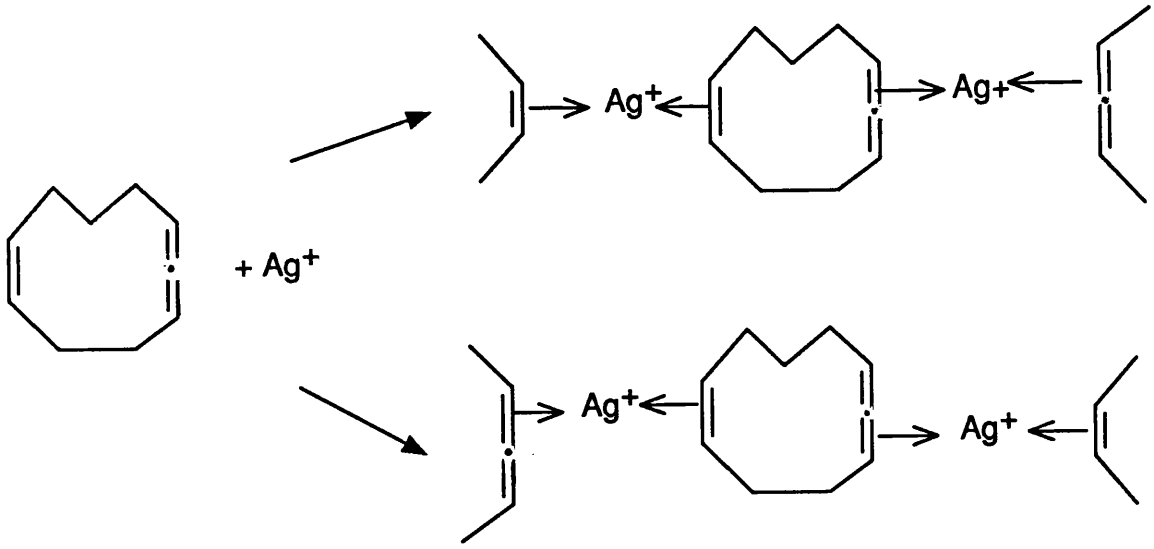
No examples have been found illustrating diastereoselective reaction or coordination of prochiral allenes with chiral electrophiles. Similarly, the interaction of electrophiles with chiral allenic substrates, where the stereogenicity is not a result of dissymmetric substitution of the allene portion itself, does not appear to have been studied.[73]

Allenic alcohols[74] and allenic amines[75] have, however, been shown to undergo highly diastereoselective cyclisation mediated by metal electrophiles (Schemes 47-49). These processes are analogous to alkenyl transformations employing mercury(II) developed by Harding[76] and Danishefsky[77].

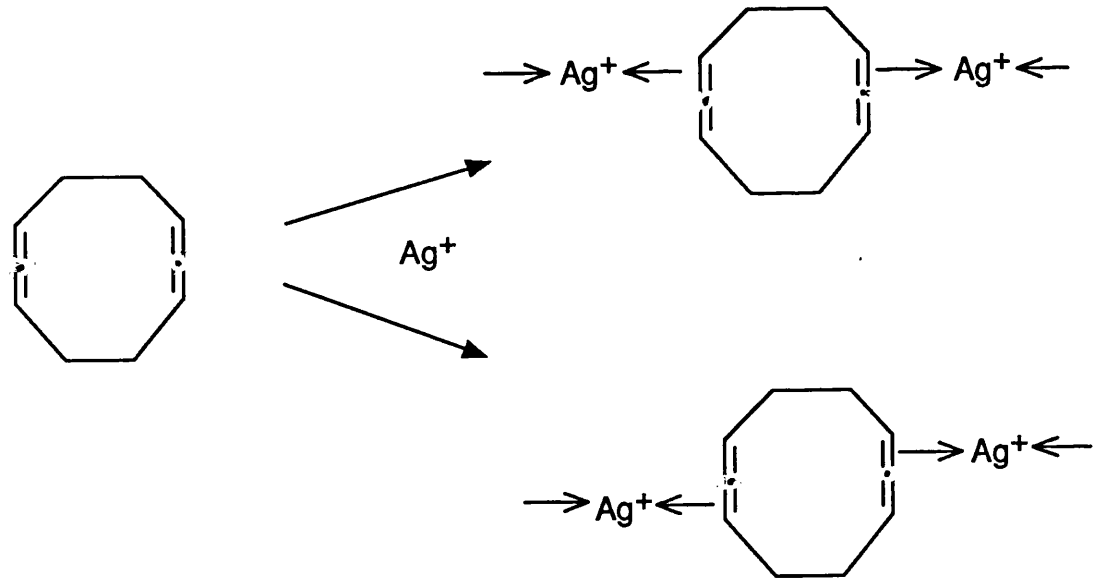


> 50 : 1
cis : trans

Scheme 49



Scheme 50

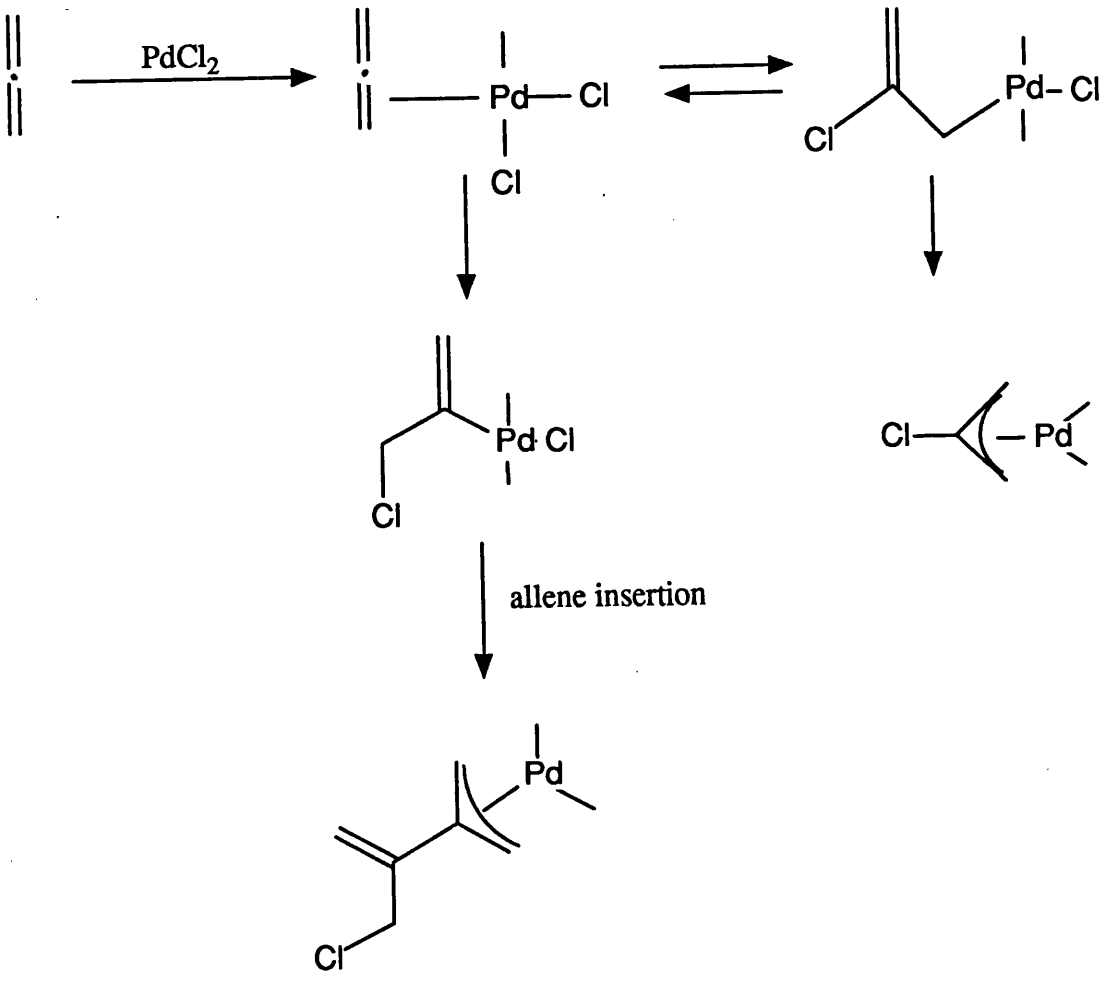


Scheme 51

This review concludes with selected examples of allene-metal coordination complexes that have been isolated and investigated[78]. The geometry of square planar metal-allene complexes was studied first in the late 1960's for their potential industrial use in polymerisation processes. A common feature[79] of the X-ray structures was the orientation of the allene perpendicular to the coordination plane.[80] The free allene is linear but, once coordinated, is found to deviate from linearity by up to 30° and bonding theories based on the Dewar-Chatt-Duncanson model for metal-olefin bonding have been proposed.[78]

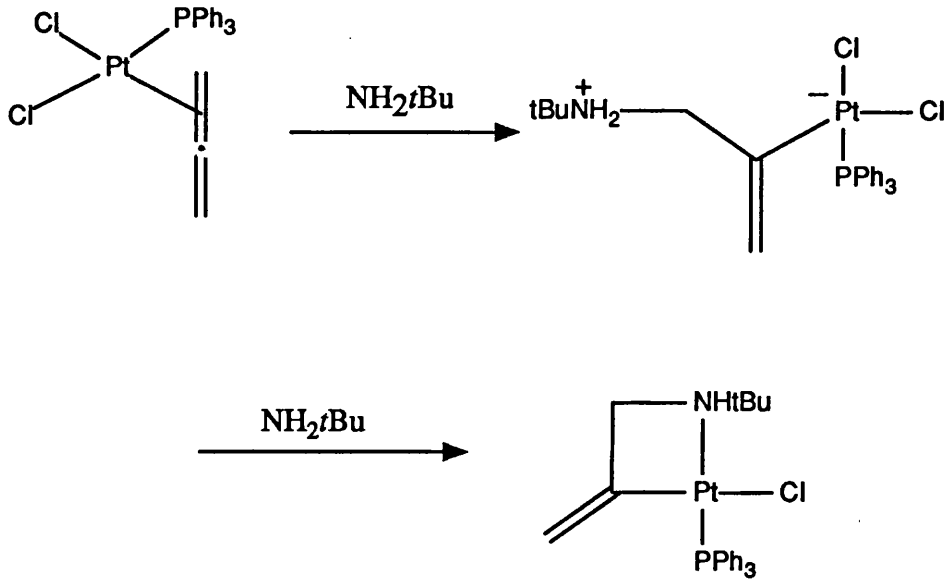
Metal-allene complexes have been studied through their IR spectra and their NMR spectra. The IR spectra of copper(I) and silver(I) complexes of cyclic allenes indicated two absorptions between 1650 and 1910 cm^{-1} corresponding to free and coordinated carbon-carbon double bonds.[81] Based on their evidence, various structures for the complexes were proposed. (Schemes 50, 51). The IR observation has since been used as a diagnostic test for coordination[82] in which it was determined that allene was a less effective coordinating ligand than ethylene towards palladium(II).

The complexes of allenes with platinum(II) and rhodium(II) have been investigated by NMR spectroscopy.[83] These studies showed upfield shifts of the allene protons and M-H coupling. However, the results could not distinguish between a σ-bonded or a metallocyclopropane structure. Fluxional behaviour was noted corresponding to intramolecular migration of the coordinated metal to alternative coordination sites on the allene. Such a phenomenon has been recognised more recently in iron-allene systems.[84]

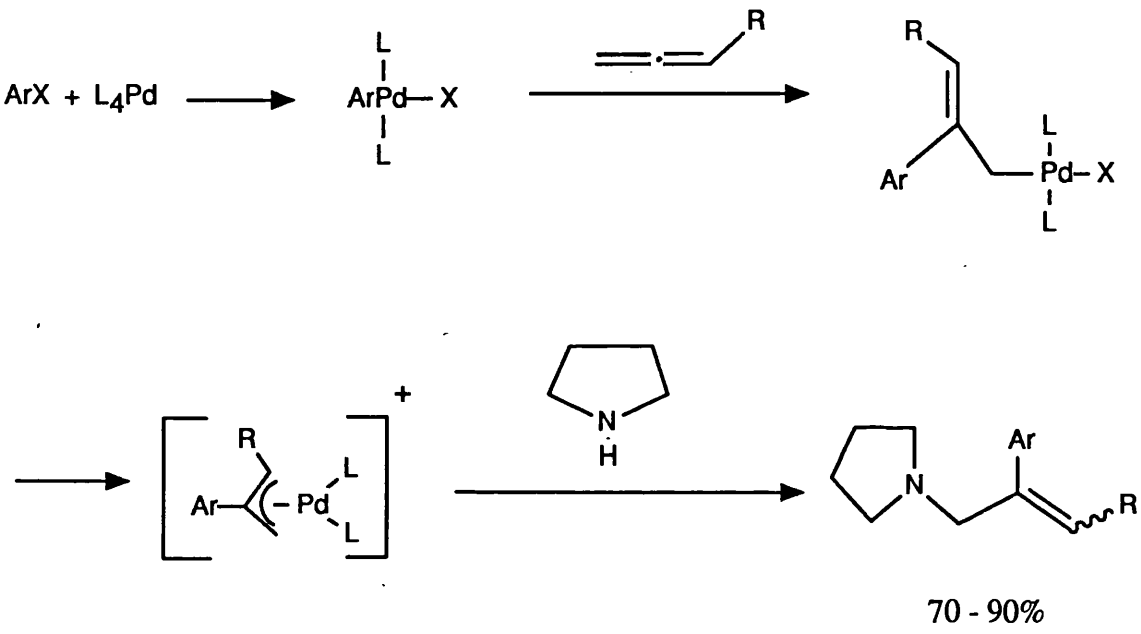


Scheme 52

Coordinated allenes have been shown to undergo reaction including hydrogenation,[85] oligomerisation/π-allyl formation (Scheme 52)[86] and amination (Scheme 53)[87]

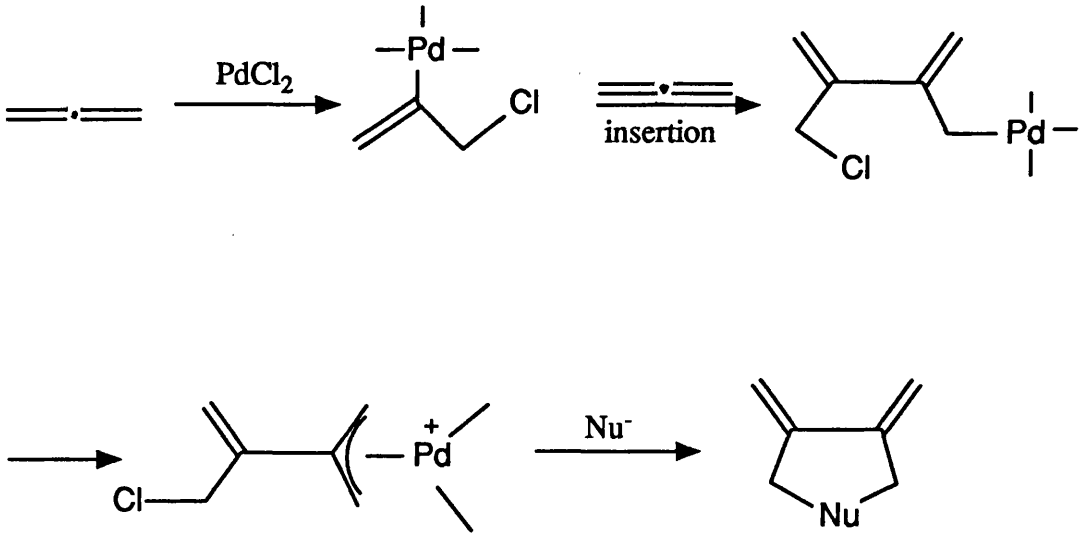


Scheme 53



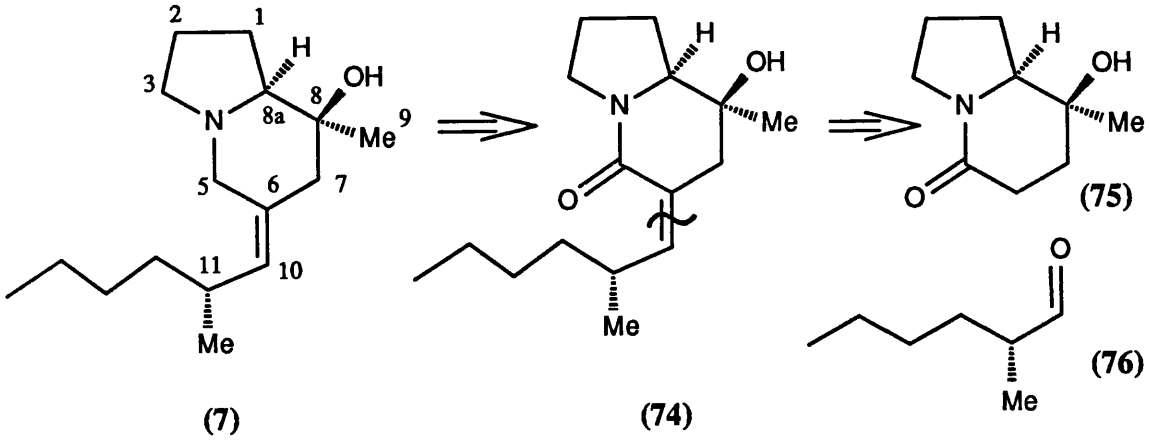
Scheme 54

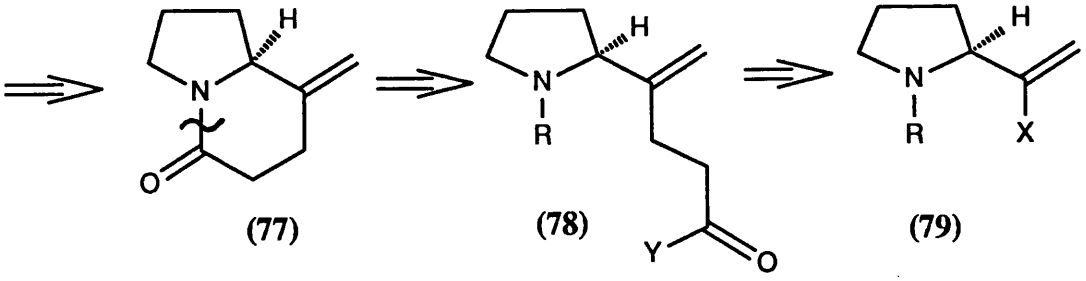
The high degree of functionalisation of products derived from reaction of allene-metal complexes has been demonstrated by Tsuji (Scheme 54)[88] and Hegedus (Scheme 55).[89] If follows, therefore, that by developing methods for face selective coordination of electrophiles by allenes, access to a wide range of highly functionalised molecules in a stereocontrolled fashion would be a valuable consequence.



Scheme 55

RESULTS AND DISCUSSION


2
1
H
3
OH
8
N
8a
Me
9
5
6
7
11
10
Me
(7)
H
OH
N
Me
O
Me
(74)
H
OH
N
Me
O
(75)
O
Me
(76)


H
N
O
(77)
H
N
R
(78)
Y
O
H
N
R
X
(79)

Scheme 56

2.1 Pumiliotoxin 251D - Synthetic Strategies

Scheme 56 illustrates the approach to be adopted towards the indolizidine natural product pumiliotoxin 251D, in a retrosynthetic analysis. A number of important structural challenges are posed by the target including:

i) Generation of the 1-azabicyclo[4.3.0]nonane system with the correct absolute stereochemistry.

ii) Introduction of the tertiary alcohol functionality at C8 with the required relative stereochemistry.

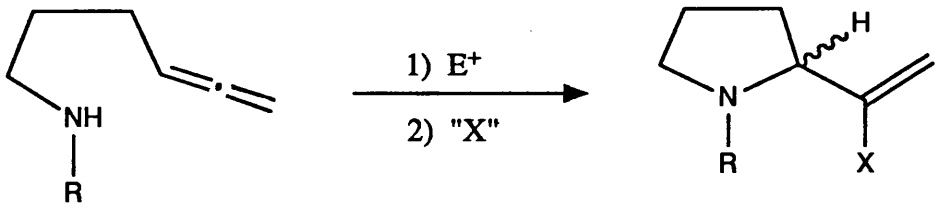
iii) Control of the C6 alkylidine side chain with Z-geometry

iv) Imposition of the (R)-absolute stereochemistry at C11.

Each of these synthetic and stereochemical issues have been addressed as part of this enantioselective total synthesis.

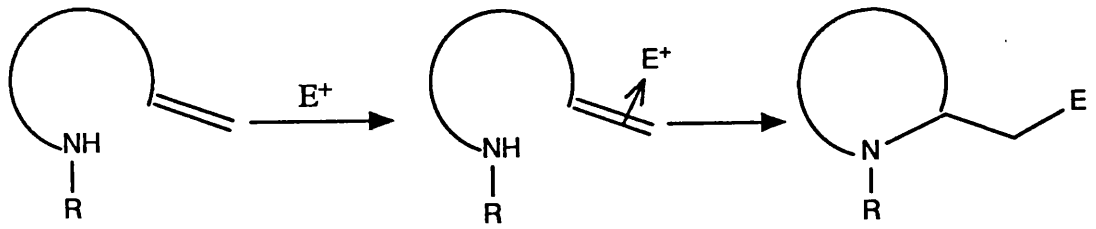
The tertiary amine target (**7**) may be derived from the corresponding Z-enelactam (**74**) by carbonyl reduction. An aldol/elimination sequence combining the key hydroxylactam (**75**) and the chiral aldehyde (**76**) would be expected to provide controlled access to (**74**) by suitable choice of elimination conditions. The hydroxylactam (**75**) is derived from the unsaturated bicyclic lactam (**77**) by stereoselective hydration of the double bond and (**77**) itself is the result of an intramolecular *N*-acylation/*N*-dealkylation sequence involving a substrate denoted in general terms by (**78**). This is accessible by routine transformations from the optically pure functionalised vinylpyrrolidine (**79**) which becomes the starting point of the total synthesis. The substituted pyrrolidine (**79**) both sets the absolute stereochemistry at the carbon atom destined to become C8a in the target, and allows further chemical manipulation to provide a rapid entry to the indolizidine skeleton.

The first half of this chapter will describe studies aimed at efficient, stereocontrolled synthesis of intermediates of the general structure **(79)** by asymmetric electrophile-promoted cyclisations of γ-allenic amines **(80)** (Scheme 57), where "X" is an appropriate electrophile. It will then be described how such intermediates have been successfully transformed into the key intermediates **(77)** and **(75)**, necessary for the proposed synthetic route. The sections towards the end of the chapter will deal with the problem of the stereocontrolled introduction of the Z-alkylidene side chain and detail the successful completion of the total synthesis. The concluding sections discuss, in brief terms, the versatility of this synthetic approach by describing a direct synthesis of the rather less complex natural product (+)-tashiromine and by illustrating the scope of the methodology described in proposed future work.

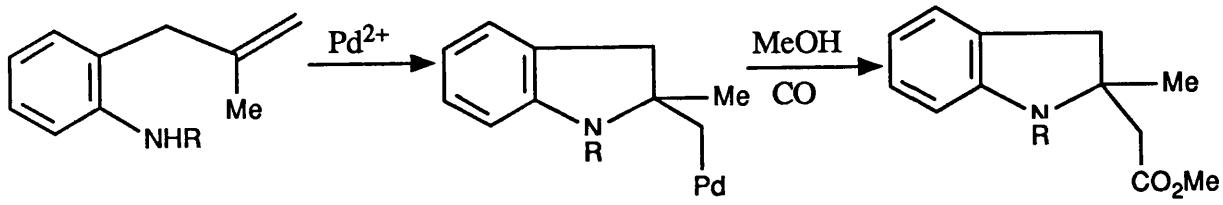


(80) **(79)**

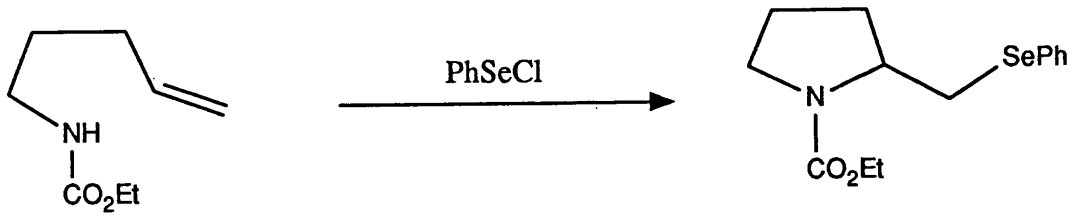
Scheme 57



Scheme 58



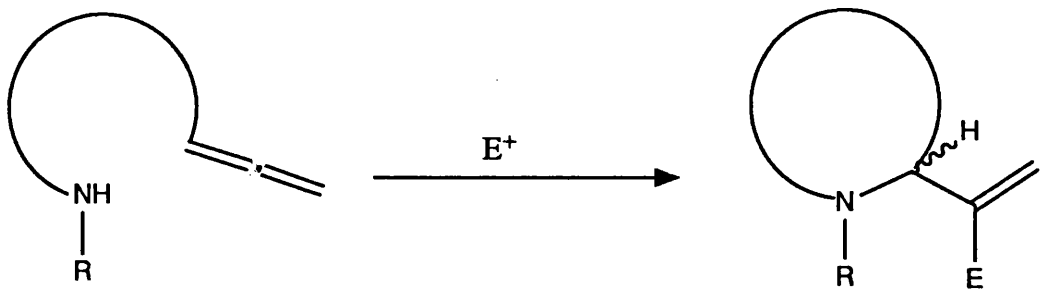
Scheme 59



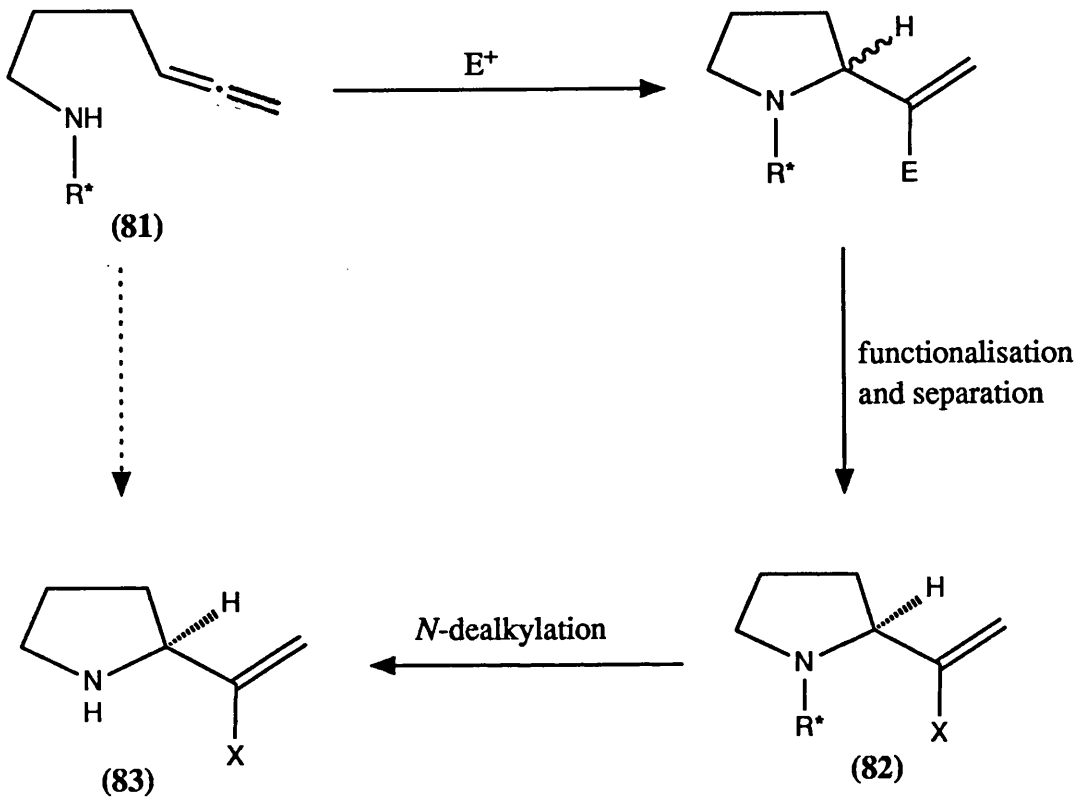
Scheme 60

2.2 An Enantioselective Approach to the Synthesis of Optically Pure Functionalised Vinylpyrrolidines

Cyclisations resulting from electrophilic π-activation of an olefinic double bond followed by attack by an internal nitrogen nucleophile offers a flexible entry into a wide range of nitrogen-containing heterocycles (Scheme 58). The use of alkenylamines in this respect has been widely documented over the last decade or so;[15,90] Schemes 59[91] and 60[92]. The approach adopted in this study, however, employs, as the source of π-electrons, an allene subunit (Scheme 61). Such a process offers two main advantages over the analogous alkenyl system. Firstly, the allene portion has a higher π-electron density than the alkene functional group. It is, therefore, more reactive towards electrophiles and so would be expected to undergo activation by a wide range of electrophilic species under relatively mild conditions. Secondly, the aminoallenes lead to more highly functionalised cyclised products than the corresponding aminoalkenes; the resultant vinylsubstituted nitrogen heterocycle is amenable to a variety of chemical manipulations. In the general cyclisation scheme (Scheme 61) a new stereogenic centre is created during the overall transformation. There is, therefore, the potential for stereochemical control and it is this aspect in particular, coupled with the two earlier points, which are examined in this enantioselective route to optically pure functionalised vinylpyrrolidines.



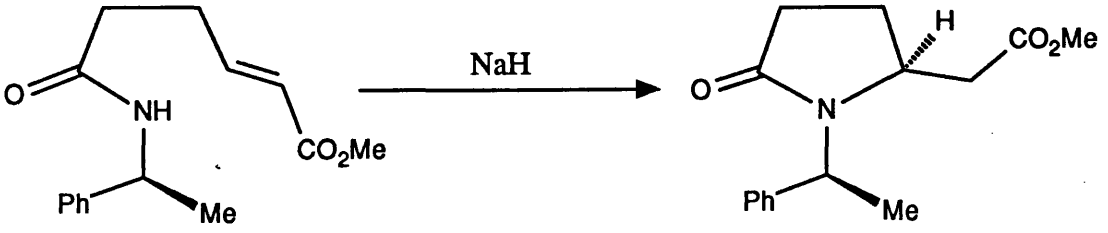
Scheme 61


E+
NH
R*
(81)
H
N
R*
E
functionalisation
and separation
H
N
H
X
(83)
N-dealkylation
H
N
R*
X
(82)

Scheme 62

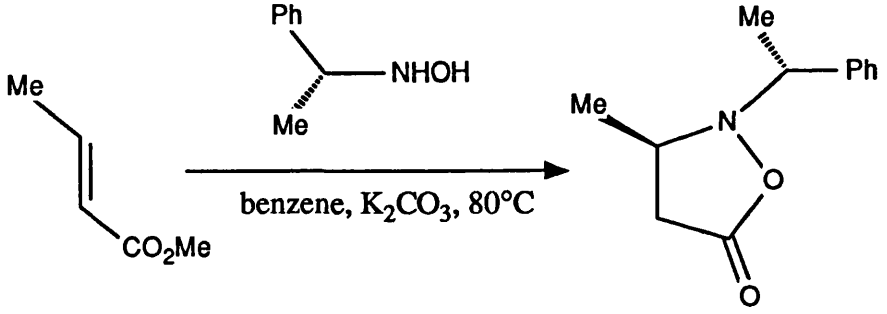
The strategy is adumbrated in Scheme 62; attachment of a chiral, non-racemic substituent R^* to the amine nucleophile in **(81)** renders the products of cyclisation diastereomeric. They are, therefore, potentially separable and following functionalisation of the cyclised intermediate, a diastereomerically- and optically pure functionalised vinylpyrrolidine product **(82)** may be isolated. Removal of the R^* control element by *N*-dealkylation affords **(83)** as a single enantiomer.

The control element R^* serves two purposes. Firstly, it acts as an internal resolving agent allowing separation of the diastereoisomers following cyclisation. Secondly, it has the potential to induce asymmetry at the newly-formed stereogenic centre, imposing a degree of diastereoselectivity in the transformation. This approach to asymmetric cyclisation, in which the control element does not form part of the newly-formed ring is one that introduces greater flexibility since in the *overall* transformation of **(81)** to **(83)**, stereochemistry has been controlled in an absolute rather than a relative sense.



44% d.e.

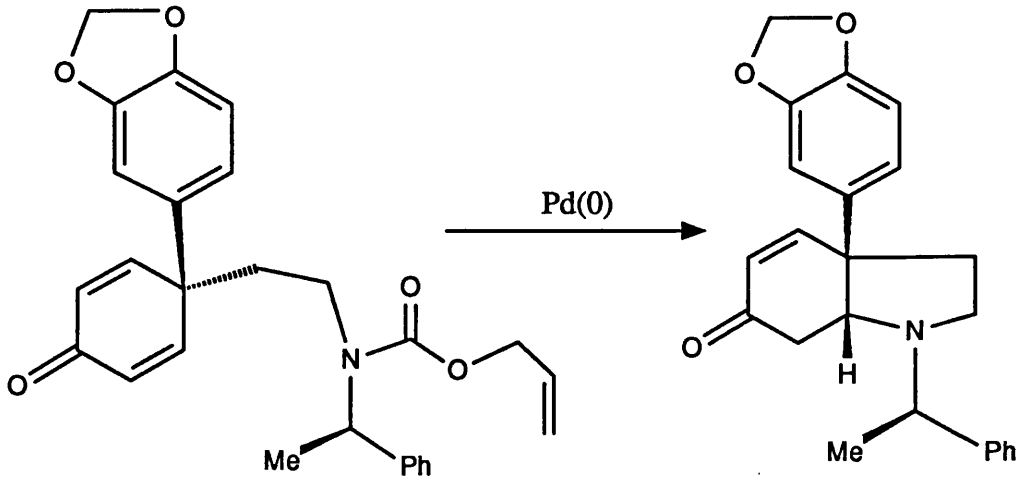
Scheme 63



60%d.e.

Scheme 64

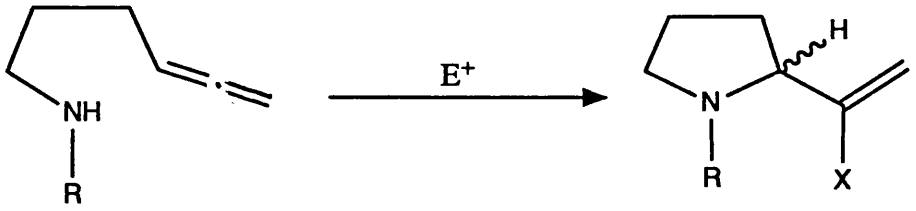
Previous studies have addressed this aspect of stereochemical control, but with few exceptions, only moderate levels of diastereoselectivity have been achieved, Schemes 63[93], 64[94]and 65[95].



17% d.e.

Scheme 65

Initial cyclisation studies were carried out using two rather different types of electrophile: silver(I) and palladium(II) (Scheme 66). Previous work in this group[96] and elsewhere[97] has demonstrated the viability of these transformations and the high degree of relative stereochemical control that may be achieved in the cyclisations. The silver(I)-mediated process results in the formation of the vinylpyrrolidine **(84)** (X=H) using catalytic quantities of electrophile; the proposed transient vinylsilver species undergoes rapid proton transfer *in situ*, releasing the active silver species back into the reaction medium. In the case of the palladium(II)-mediated process, under carbomethoxylation conditions, the product obtained is the synthetically more versatile acrylate methyl ester **(84)** (X = CO_2Me). The reaction is, once again, catalytic with respect to the active electrophilic palladium(II), when stoichiometric quantities of copper(II) chloride are present as a catalyst reoxidant. The next section describes the range of cyclisation substrates employed in this study and their synthesis.

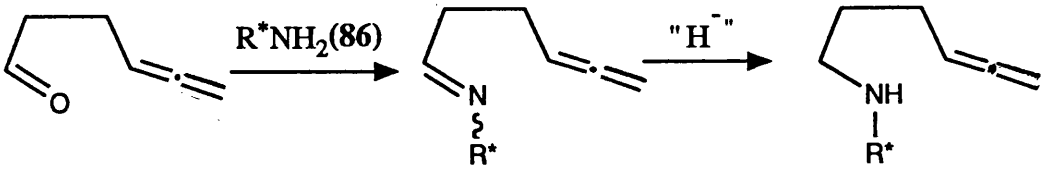


(84)

$E^+ = Ag^+$ X = H

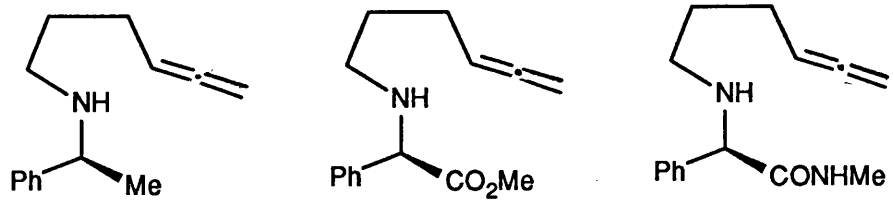
$E^+ = Pd^{2+}$, CO, MeOH, $CuCl_2$ X = CO_2Me

Scheme 66

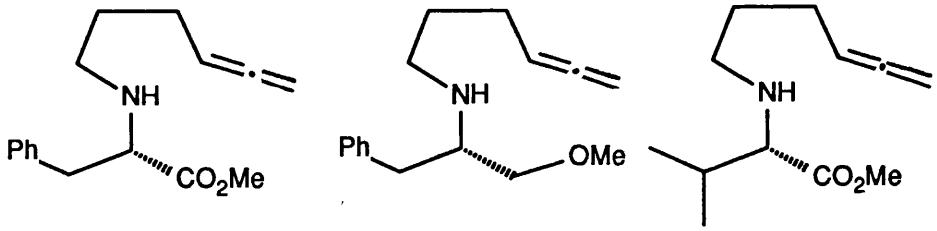


(85) (87) (81)

Scheme 67

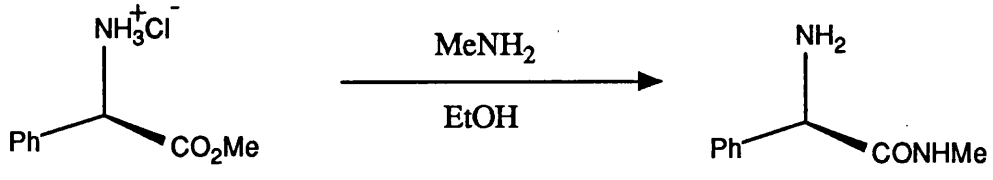


(88) (89) (90)



(91) (92) (93)

Figure 6



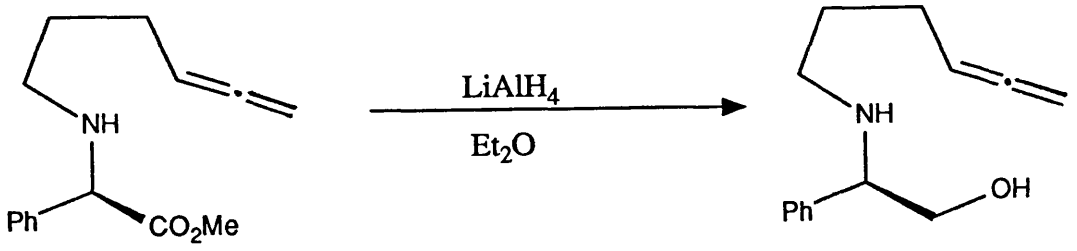
(94) (95)

94%

Scheme 68

2.3 The Cyclisation Substrates

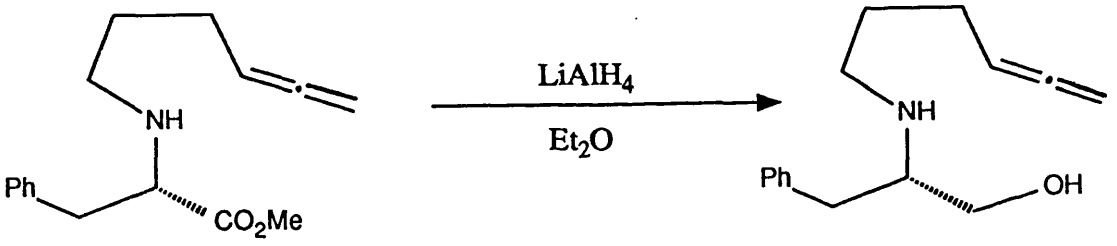
Scheme 67 illustrates the reductive amination sequence employed for the synthesis of the allenic amine substrates (**80**). The allenic aldehyde (**85**) was readily prepared by reduction of 4,5-hexadienitrile with DiBAl followed by acidic hydrolysis.[98] Access to multigram quantities of the nitrile could be achieved in 22% yield from triethyl orthoacetate employing literature conditions.[99] Combination of (**85**) with the appropriate chiral amine (**86**) in ether, in the presence of a drying agent, followed by reduction of the resulting imine (**87**) with sodium borohydride in methanol or ethanol, afforded moderate (20-50%) but reproducible yields of the required allenic secondary amine (**81**).[100] Figure 6 illustrates the range of optically pure allenic substrates that were derived by this method. The chiral primary amines required for (**88**) to (**93**) were readily available either as commercial (S)-α-methylbenzylamine or following standard chemical manipulation of common amino acid derivatives. The methyl ester hydrochloride salts of (R)-phenylglycine, (S)-phenylalanine and (S)-valine were prepared from the corresponding amino acids in high yield (75-95%) according to the method of Meyers[101] (thionyl chloride/methanol), with no significant racemisation.[102] These were used in the preparation of (**89**), (**91**) and (**93**) respectively. *O*-Methylphenylalaninol, the precursor for (**92**), was obtained from (S)-phenylalaninol by treatment with sodium in benzene followed by methylation with methyl iodide.[103] Bulb-to-bulb distillation followed by treatment with ethereal HCl afforded, on recrystallisation, the hydrochloride salt. The amino amide (**95**), required for (**90**), was obtained in 94% yield by aminolysis of (**94**) in ethanol with no apparent racemisation, as reported by Seebach[104] (Scheme 68).



(89) **(96)**

87%

Scheme 69



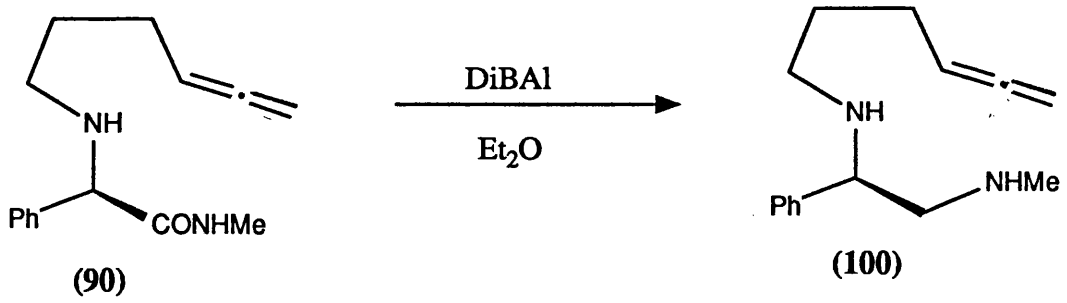
(91) **(97)**

36%

Scheme 70

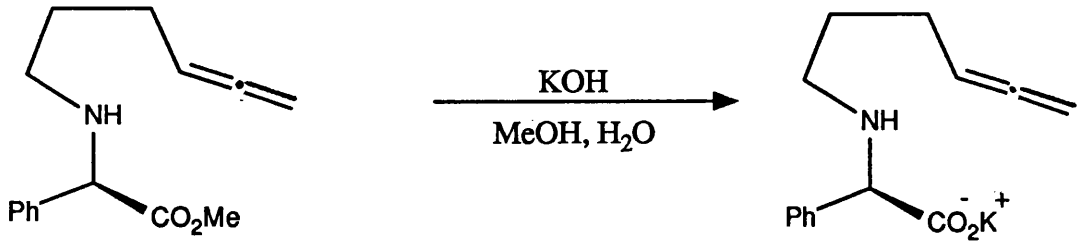
A number of additional allenic amine cyclisation substrates could now be derived from this group of amino esters and amides (Schemes 69-73) by simple functional group manipulation. Phenylglycine-based substrates constitute the majority of those synthesised since the inherent *N*-benzyl residue renders the cyclised product readily amenable to *N*-dealkylation at a later stage.

The amino alcohols **(96)** and **(97)** were the products of ester reduction of **(89)** and **(91)** using lithium aluminium hydride in ether, such processes having been shown previously to proceed without observable racemisation.[105] Although resistant to reduction by lithium aluminium hydride, the amino amide **(90)** was transformed smoothly to the diamine **(100)** when DiBAl was employed as the reducing agent. The superiority of this reagent with such substrates has been noted previously.[106]



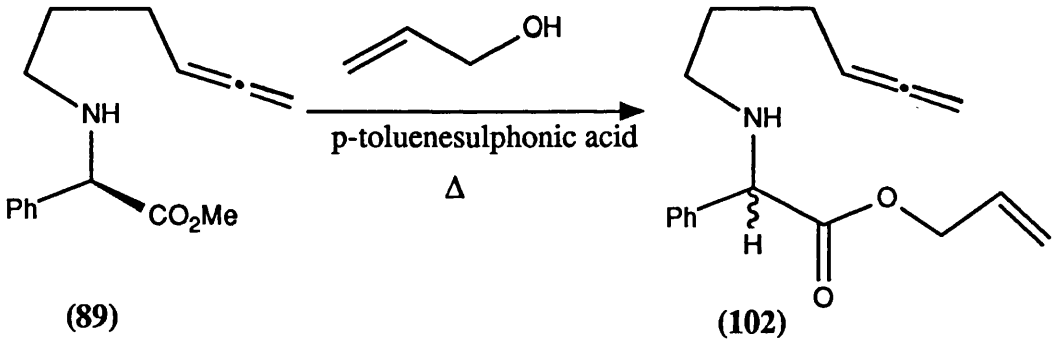
(90) → **(100)** 95%

Scheme 71



(89) (101)

Scheme 72

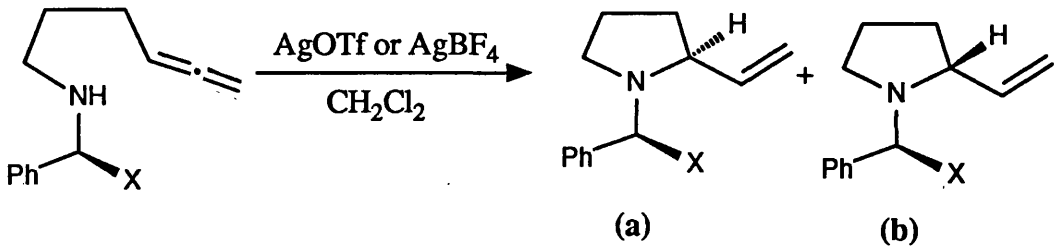


(89) (102)

52%

Scheme 73

The carboxylate salt (**101**) was prepared simply by stirring the methyl ester (**89**) with an excess of potassium hydroxide in aqueous methanol. The product was used without further purification other than evaporation, dilution with dichloromethane followed by filtration; complete reaction was indicated by the absence of a methyl singlet in the proton NMR spectrum. The allyl ester (**102**) was derived from (**89**) in moderate yield by a transesterification procedure which led to optically inactive material and so would appear to have been accompanied by racemisation. For the determination of the diastereoselectivity of cyclisation of this substrate, however, loss in optical purity was irrelevant. The following four sections describe the use of these cyclisation substrates in electrophile-mediated transformation and how the diastereoselectivities may be related to the functionality associated with the allenic amine.



Scheme 74

Entry	Allenic amine	Products	Mol% Ag(I)	(a):(b)[1] (d.e.)	Yield
1	(88)	(103a,b)	46%	2:1 (33%d.e.)	87%
2	(89)	(104a,b)	62%	4:1 (60%d.e.)	71%
3	(90)	(105a,b)	50%	9.3:1 (81%d.e.)	90%
4	(96)	(106a,b)	15%	4:1 (60%d.e.)	90%
5	(100)	(107a,b)	45%	8:1 (78%d.e.)	63%
6	(102)	(108a,b)	31%	4:1 (60%d.e.)	77%

1 : The relative stereochemistry of the major and minor products (a) and (b) have been shown by X-ray crystallography and chemical correlation to be those indicated in Scheme 74 for entries 2-6.

Table 1

2.4 The Silver(I)-Mediated Cyclisation

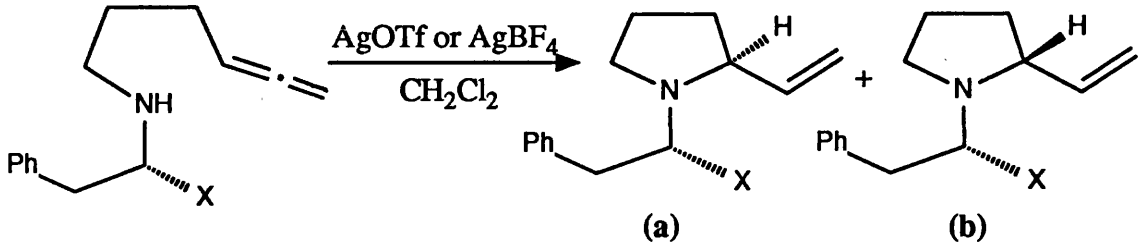
2.4(i) The silver(I)-mediated cyclisation of the allenic amine substrates was carried out at room temperature, under light-free conditions, employing either silver triflate or silver tetrafluoroborate as the electrophilic trigger and dichloromethane as the solvent of choice. The selection of silver salt did not appear to alter the stereochemical course of the transformation although other factors, namely the solvent or the molar proportion of silver salt used, did have an influence (*vide infra*). The reactions were, in general, complete within 3h and the diastereoselectivity was determined by comparison of integrals for appropriate signals in the proton NMR spectrum of the reaction mixture following aqueous work-up. Where necessary, further purification of the product 2-vinylpyrrolidines was subsequently carried out by column chromatography. The results of the cyclisation study, in terms of the yield of products and the diastereoselectivity, are presented in Tables 1,2 and 3.

The cyclisation of the α-methylbenzyl and phenylglycine-based derivatives (Table 1) follows a clear trend in which the observed diastereoselectivity increases with the ability of the residue X to complex silver(I);[107] thus diastereoselectivity increases as X varies in the following order.

$$Me < CO_2R \approx CH_2OH < CONHMe \approx CH_2\,NHMe$$

The high chemical yield of cyclised products is a common feature of these silver(I)-mediated cyclisations.

The results of the phenylalanine-based derivatives (Table 2) indicate a similar trend where the alcohol functionality present in **(97)** effects a greater degree of stereochemical control in the transformation (60% d.e) compared with the analogous cyclisations of the methyl ester **(91)** (9%d.e.) or methyl ether **(92)** (9% d.e.). Most noticeable, however, is the diminished diastereoselectivity compared with the phenylglycine-derived substrates.

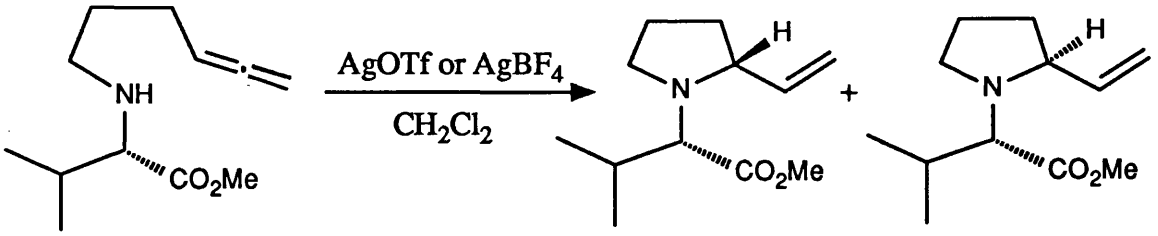


Scheme 75

Entry	Allenic amine	Products	Mol% Ag(I)	(a):(b)[1] (d.e.)	Yield
1	**(91)**	**(110a,b)**	140%	1.2:1 (9%d.e.)	100%
2	**(92)**	**(109a,b)**	170%	1.2:1 (9%d.e.)	83%
3	**(97)**	**(111a,b)**	320%	4:1 (60%d.e.)	64%

1 : Relative stereochemistry of products (a) and (b) not determined.

Table 2



(93) (112a) (112b)

Scheme 76

Entry	Mol% Ag(I)	(a):(b)[1] (d.e.)	Yield
1	190%	2:1 (33%d.e.)	90%
2	40%	3:1 (50%d.e.)	70%
3	20%	4:1 (60%d.e.)	55%

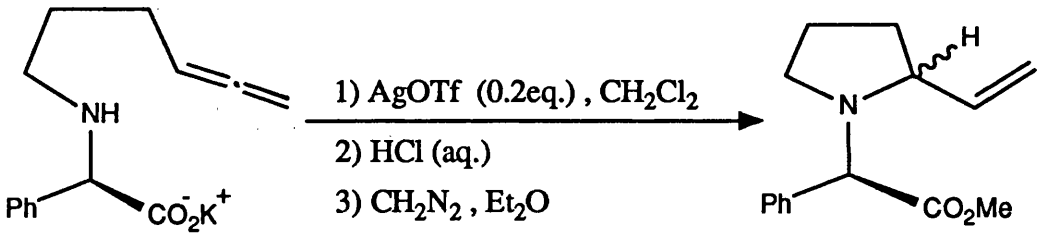
1 : Relative stereochemistry of products (a) and (b) not determined.

Table 3

To examine this issue further, the valine methyl ester derivative **(93)** was synthesised and subsequent cyclisation afforded products **(112a,b)** with diastereoselectivities which were, in general, lower than for **(89)** (see Table 3). These results would seem to suggest the presence of the phenyl substituent common to the phenylglycine derivatives (rather than the benzyl or isopropyl groups in **(91)** and **(93)**) was a factor in ensuring a reasonable degree of diastereoselectivity. Such an interpretation, however, must be accompanied by the caveat that these systems have product distributions corresponding to energy differences of less than $3KJmol^{-1}$ so such conclusions should be treated with caution.

The carboxylate (**101**) would, it was hoped, provide a highly effective means of coordination to the silver(I) electrophile and, by extrapolation from the established trend, lead to the corresponding cyclised products with high stereoselectivity.

Employment of the reaction sequence illustrated in Scheme 77, in which the intermediate cyclised carboxylate salts underwent methyl ester formation by addition of diazomethane following acidification, afforded a 4:1 mixture of cyclised ester (**104a,b**). Thus, the presence of the carboxylate functionality offered no improvement, in terms of diastereoselectivity, over the use of the ester (**89**) or the alcohol (**96**).



(101)

(104a,b)
4 : 1

Scheme 77

Entry	Allenic amine	Products	Mol% Ag(I)	(a):(b) (d.e.)	Yield
1	(89)	(104a,b)	20%	4.3:1 (62%d.e.)	88%
2	(89)	(104a,b)	40%	3.7:1 (57%d.e.)	71%
3	(89)	(104a,b)	62%	4:1 (60%d.e.)	71%
4	(90)	(105a,b)	23%	5.5:1 (69%d.e.)	89%
5	(90)	(105a,b)	50%	9.3:1 (81%d.e.)	90%
6	(90)	(105a,b)	90%	5:1 (67%d.e.)	94%
7	(100)	(107a,b)	38%	6.3:1 (73%d.e.)	89%
8	(100)	(107a,b)	45%	8:1 (78%d.e.)	63%
9	(100)	(107a,b)	57%	9:1 (80% d.e.)	n.d.

n.d. : Yield not determined.

Table 4

2.4(ii) Variation in diastereoselectivity with molar proportion of silver(I) and solvent

An observation that first became evident with the results shown in table 3 was the occasional variation in diastereoselectivity as the molar proportion of silver(I) salt was changed. This property was studied more fully with the phenylglycine-based derivatives and the results are shown in Table 4. For the methyl ester substrate (**89**), no significant variation in product distribution was seen as the proportion of silver(I) salt was varied (entries 1-3). However, for the amide and amine derivatives (**90**) and (**100**)) (entries 4-6 and 7-9) there was a marked effect on diastereoselectivity with optimal levels observed using approximately 50 mol% of silver(I). Such variations suggest that the key step of the cyclisation may not simply involve a bimolecular process but that a second amine molecule could participate.

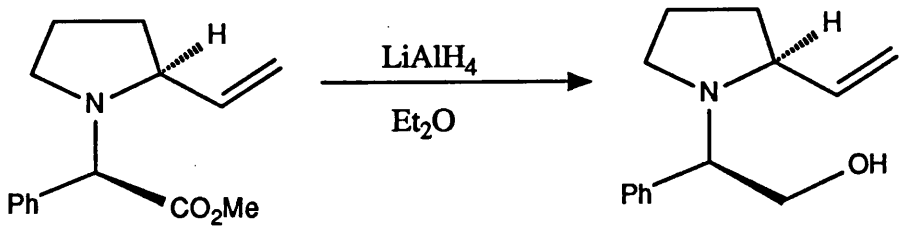
Entry	Allenic amine	Products	Solvent	Mol% Ag(I)	(a):(b) (d.e.)	Yield
1	**(89)**	**(104a,b)**	Acetone	31%	3:1 (50%d.e.)	90%
2	**(89)**	**(104a,b)**	DMSO	42%	4.7:1 (65%d.e.)	85%
3	**(89)**	**(104a,b)**	$MeOH/H_2O$ (3:2)	29%	1.1:1 (5%d.e.)	86%
4	**(100)**	**(107a,b)**	DMSO	54%	4:1 (60%d.e.)	90%

Table 5

An additional phenomenon that has been noted with the silver(I)-mediated process is the variation in diastereoselectivity when the reaction is carried out in a range of solvents. The results of this study are presented in Table 5 and indicate that for the methyl ester **(89)**, clean conversion to **(104a,b)** occurs in acetone, DMSO and aqueous methanol. In this latter case, the silver salt used was silver nitrate (for solubility purposes) and almost complete loss of diastereoselectivity was noted (entry 3). The improvement in product ratio in DMSO (compared with entry 2, Table 1) was encouraging although this did not translate to the cyclisation of the diamine **(100)** (entry 4).

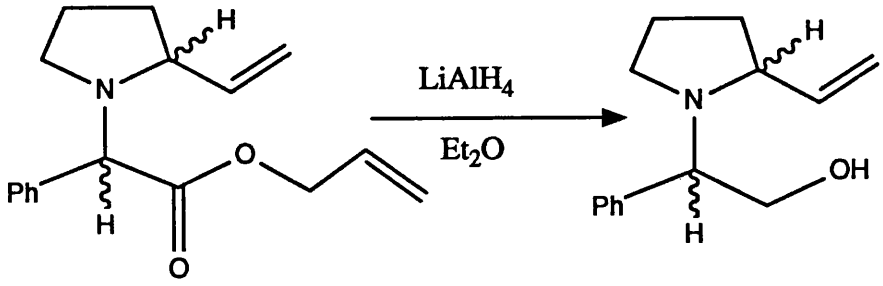
2.4(iii) Influence of temperature on Diastereoselectivity

As will be discussed in section 2.4.(v), the observed diastereoselectivities are proposed to be the result of kinetic phenomena. For this reason, the cyclisation of the diamine substrate **(100)** was carried out in dichloromethane at temperatures ranging from -78°C to -10° in order to monitor any improvement in diastereoselectivity that might have resulted. In the event, although the reaction rate was reduced significantly (incomplete reaction after 10h), no improvement in product ratio could be discerned.



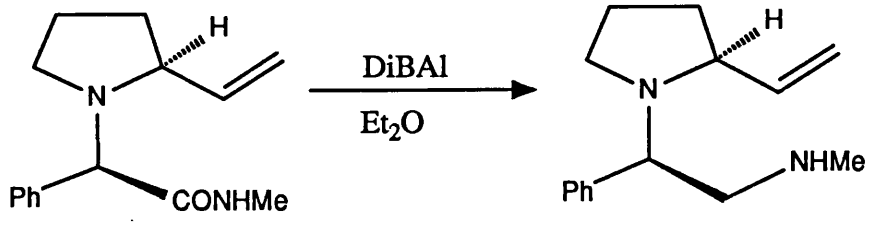
(104a) **(106a)**
89%

Scheme 78



(108a,b) (4:1) **(106a,b)** (4:1)
92%

Scheme 79

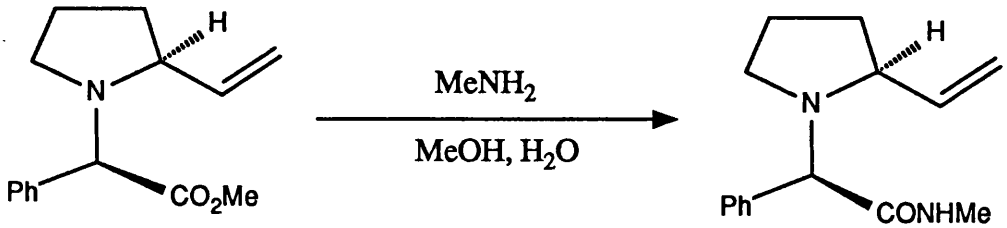


(105a) **(107a)**
78%

Scheme 80

2.4(iv) Stereochemical Assignment of Major Products.

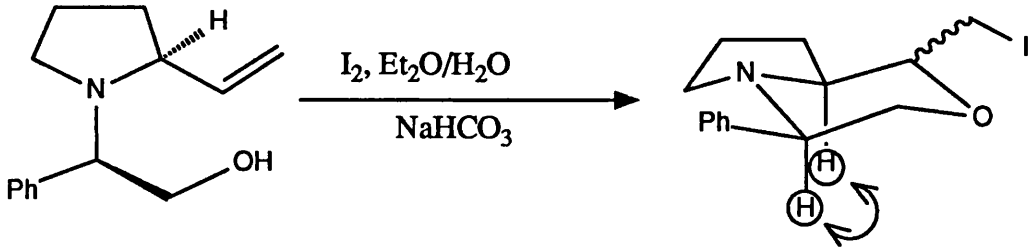
The sense of asymmetric induction in the cyclisations of each of the phenylglycine-derived substrates **(89)**, **(90)**, **(96)**, **(100)**, and **(102)** has been shown by chemical correlation, using standard functional group transformations, to be the same (Schemes 78-81). Thus, treatment of the major product of cyclisation of the ester **(89)** with lithium aluminium hydride afforded **(106a)**, the major product of cyclisation of the alcohol **(96)**, as a single diastereoisomer. Similar treatment of the (4:1) product mixture following cyclisation of the allyl ester **(102)** afforded a 4:1 mixture of alcohol products, with **(106a)** predominating. Reduction of the 9:1 mixture of cyclised amides **(105a,b)** with DiBAl yielded the cyclised amines **(107a,b)** in a similar ratio. The major ester product **(104a)** was correlated with the major cyclised amide **(105a)** by aminolysis which proceeded with no apparent epimerisation.



(104a) **(105a)**
47%

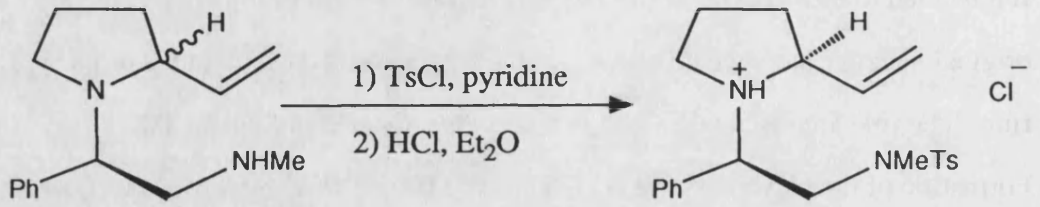
Scheme 81

It remained to establish the relative stereochemical relationship between the original benzylic stereogenic centre and the newly-formed centre at C2 of the ring. The first approach taken in this respect is indicated in Scheme 82. Formation of the bicyclic system **(113)** derived from **(106a)** by iodoetherification[108] would, it was hoped, allow stereochemical assignment on the basis of nOe experiments. Although the reaction proceeded smoothly, isolation of the material was precluded by the instability of the amine-alkyliodide combination towards polymerisation. A related approach, employing a phenylselenoetherification procedure,[109] also proved unsuccessful.



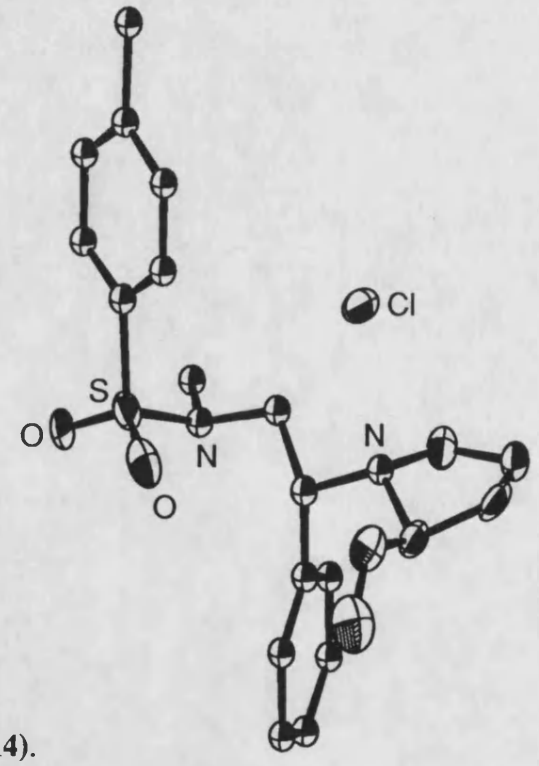
(106a) **(113)**

Scheme 82



(107a,b) (9:1) **(114)**

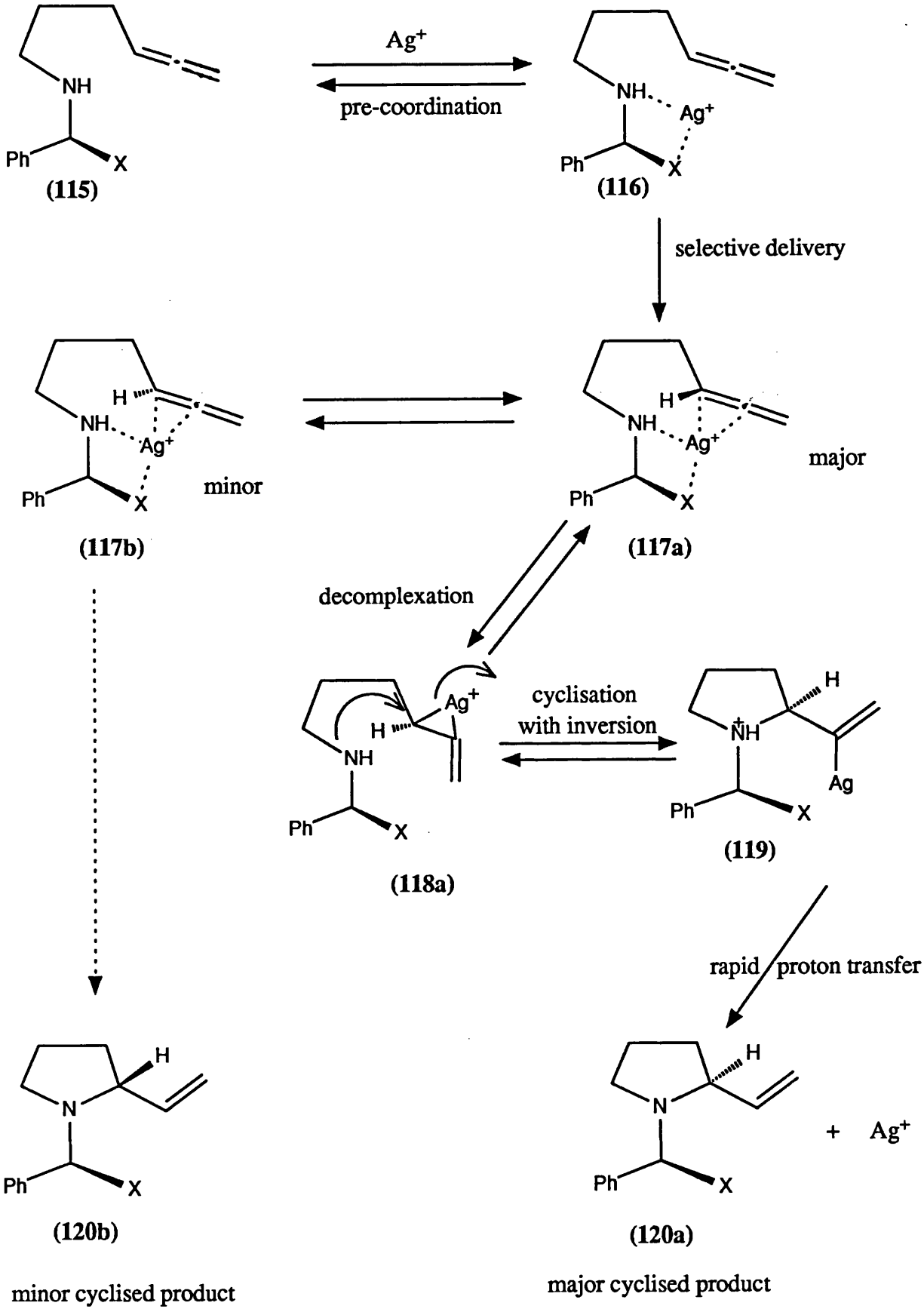
Scheme 83



ORTEP diagram for **(114)**.
Thermal ellipsoids represent 33% probability

Figure 7

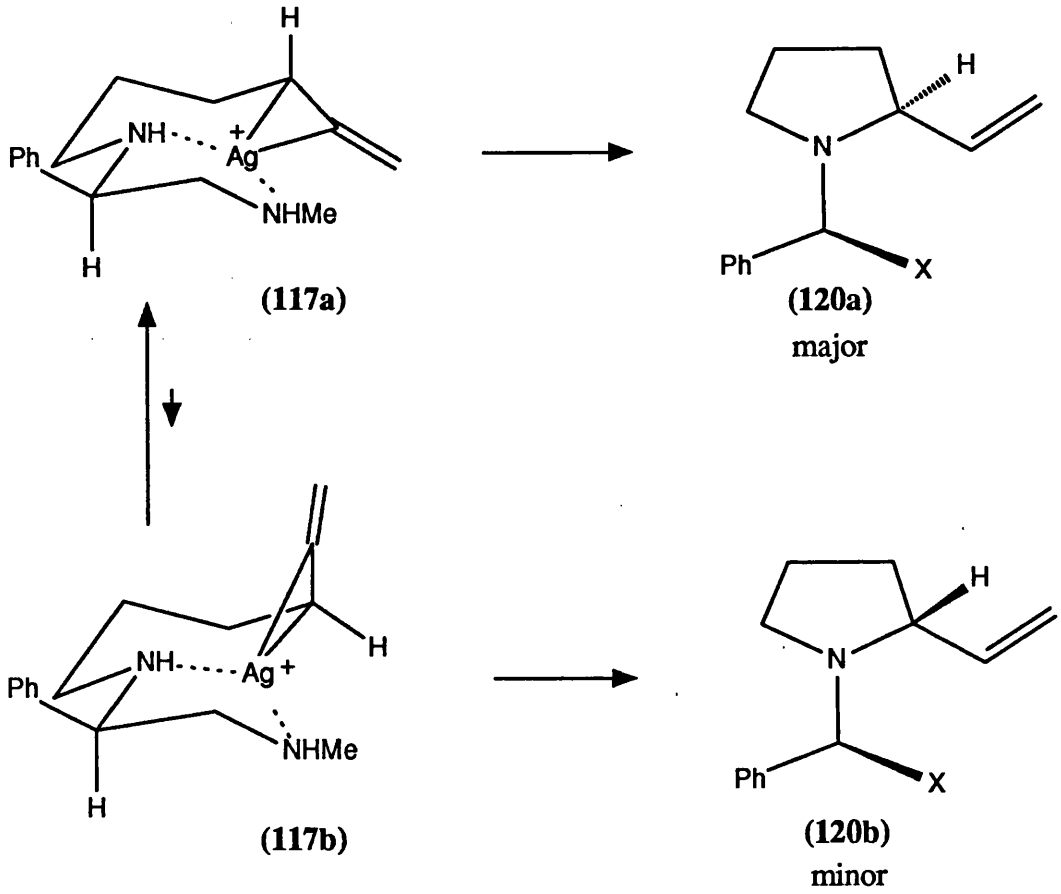
Following these initial efforts, it was decided to obtain a crystalline derivative of a major cyclised product, suitable for X-ray analysis. Although recrystallisation of the hydrochloride salt of the 9:1 mixture **(107a,b)** failed to afford crystals of sufficient quality for analysis, success was achieved by employing the sequence described in Scheme 83. Treatment of the mixture **(107a,b)** with *p*-toluenesulphonyl chloride in pyridine, followed by addition of ethereal HCl afforded, on recrystallisation from dichloromethane/ethyl acetate/cyclohexane the corresponding hydrochloride salt **(114)**. The X-ray structure is shown in Figure 7. Since the absolute stereochemistry of the phenylglycine-based portion is established as (R), the structure allows assignment of stereochemistry at the newly-formed centre as (S). The chemical correlation studies enable this assignment to be applied to the remaining cyclised phenylglycine derivatives.


Ag+
pre-coordination
(115)
(116)
selective delivery
minor
major
(117b)
(117a)
decomplexation
cyclisation
with inversion
(118a)
(119)
rapid proton transfer
(120b)
(120a)
+ Ag+
minor cyclised product
major cyclised product

Scheme 84

2.4(v) Proposed Mechanisms for the Silver(I)-Mediated Cyclisation

On the basis of the observed trend in cyclisation diastereoselectivity as the functionality of the chiral amine residue is varied, two alternative mechanistic interpretations may be offered. These arguments are illustrated for the phenylglycine-based substrates **(115)** but are equally relevant to cyclisations of the valine- and phenylalanine-derived analogues. Scheme 84 illustrates the first of these two mechanisms in which precoordination of the silver(I) electrophile by a combination of the amine nucleophile and the X group present in the control element is suggested as shown in **(116)**. Such an interaction may then result in selective delivery of the electrophile preferentially to one of the two available diastereotopic faces of the allene subunit to form an intermediate metallocyclopropane cation **(117a,b)**. Subsequent backside displacement (with inversion) by the amine nucleophile would result from decomplexation followed by rotation of the metallocyclopropane portion in **(118a)**. The short-lived vinylsilver product **(119)** undergoes rapid and irreversible proton transfer to afford the major vinylpyrrolidine **(120a)** with concomitant release of the electrophile. The stereochemistry of the final product, therefore, is set at the stage of initial complexation of the silver ion by the allene π-system. Such an interpretation has been invoked previously in electrophile-mediated additions to chiral, non-racemic allenes where no racemisation is detected.[110, 73a,b] It would seem reasonable that the degree of stereocontrol of this process, should it proceed *via* this postulated mechanism, would depend on the efficiency of the initial precoordination to the silver ion. This, in turn, would improve as the ability of the group X to coordinate the electrophile increases. Such a scenario would explain the observed trends in diastereoselectivity although the solvent and concentration dependence is less obvious. It is possible that the decomplexation of the metallocyclopropane from the amine nucleophile,

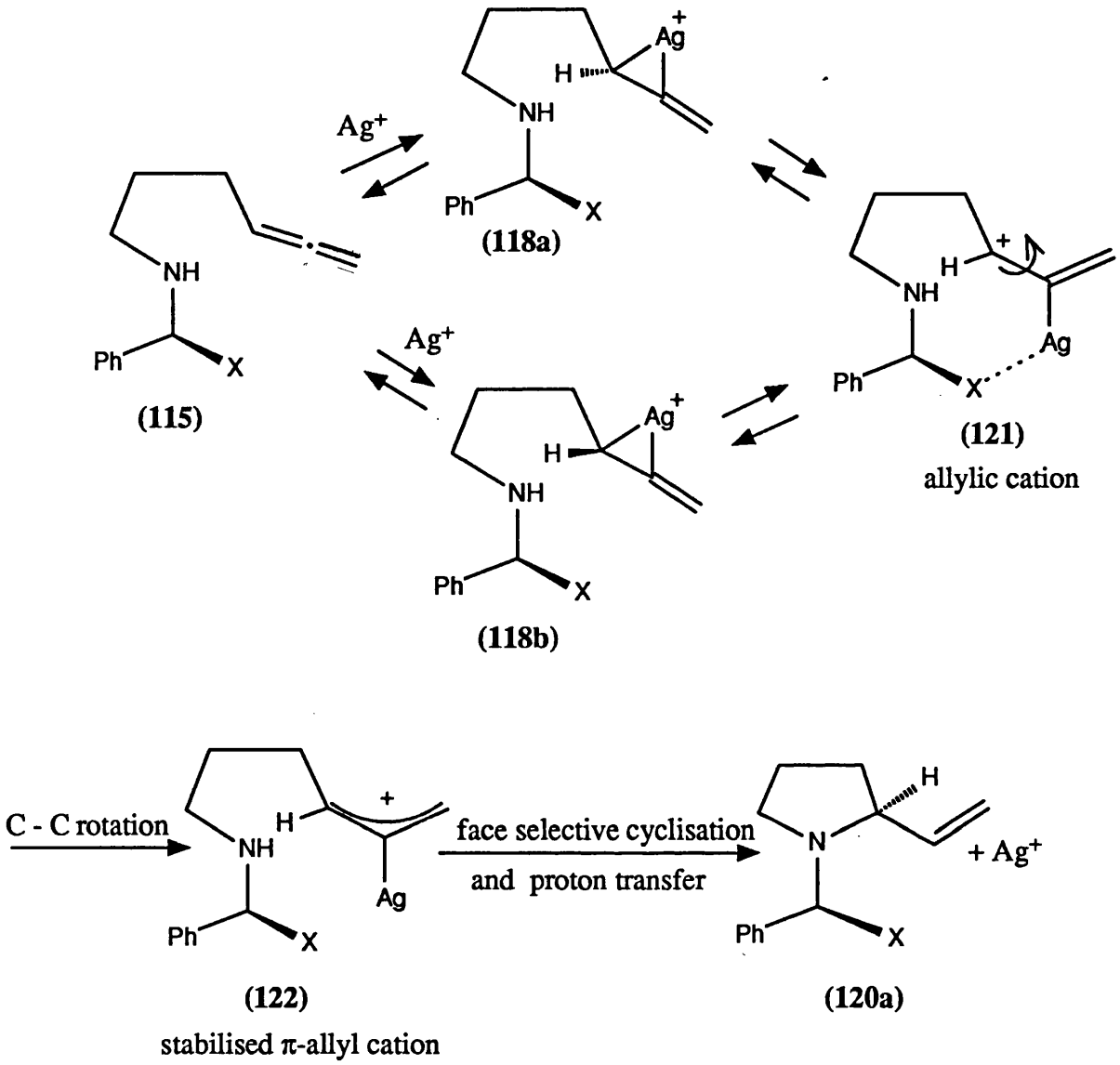

H
NH
Ag
+
Ph
NHMe
H
(117a)
H
N
Ph
X
(120a)
major
H
NH
Ag +
Ph
NHMe
H
(117b)
H
N
Ph
X
(120b)
minor

Scheme 85

necessary for subsequent cyclisation to occur, is aided by stabilisation of the silver species in the form of intermolecular coordination. Thus, a second amine molecule could be responsible for triggering this decomplexation/cyclisation sequence and such an effect might be expected to be sensitive to concentration and/or solvent variations.

This idea may be taken a step further to account for the observed sense of diastereoselectivity (Scheme 85). The complexes **(117a)** and **(117b)** are considered to exist as equilibrating diastereomeric species both in pseudo-*trans*-decalin conformations with the phenyl substituent locked in a pseudo-equatorial orientation. The geometry of the silver ion is deemed to be square planar for convenience of representation. **(117a)**, with the vinyl group pseudoequatorial and the hydrogen atom in a pseudoaxial orientation, would be expected to predominate and subsequent cyclisation results in the major product **(120a)** with (S)-absolute stereochemistry at the newly-formed asymmetric centre.

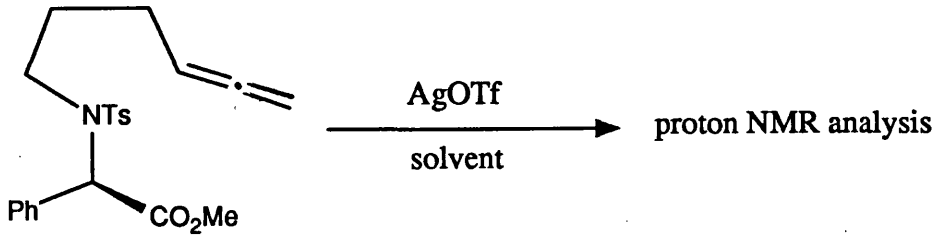
This crude model, therefore, has been successful in rationalising both the pattern and sense of asymmetric induction observed.


Ag+
NH
Ph
X
H
(115)
(118a)
(118b)
(121)
allylic cation

C - C rotation
face selective cyclisation
and proton transfer
+ Ag+
(122)
stabilised π-allyl cation
(120a)

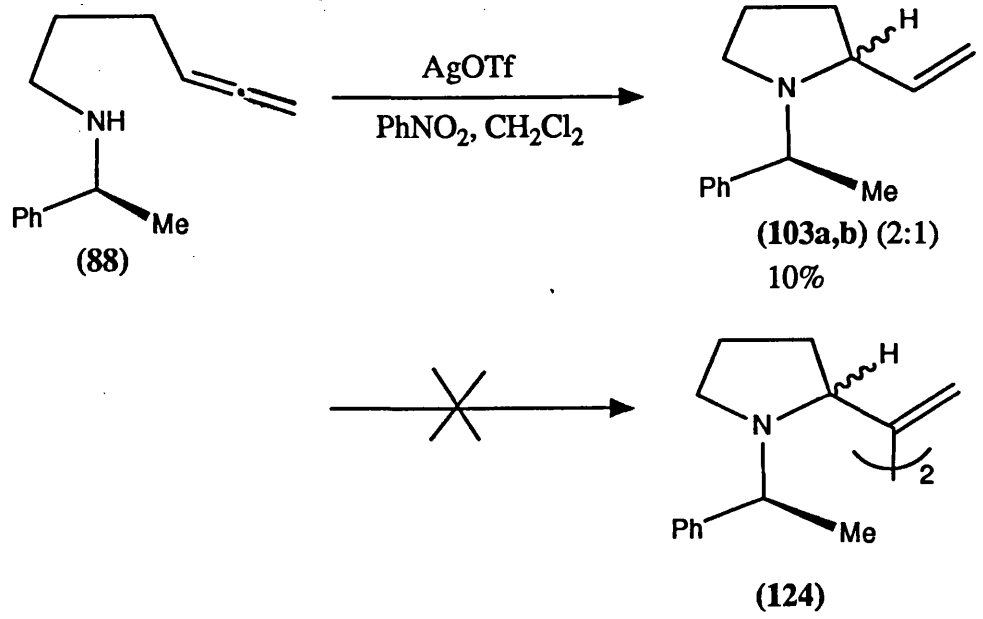
Scheme 86

There is, however, an alternative mechanistic sequence which is outlined in Scheme 86 and involves initial non-selective interaction of the silver ion with the allene π-system to form the intermediate metallocyclopropane cations **(118a,b)**. These may undergo irreversible isomerisation to form the common σ-silver-π-allyl cation **(122)** in which two stabilising interactions may be distinguished. Firstly, the open form of the metallocyclopropane **(121)** is stabilised by interaction between the X group of the chiral *N*-substituent and the σ-bonded silver species. Secondly, the positive charge in **(121)** is stabilised by overlap of the empty p orbital with the neighbouring π-system, following 90° carbon-carbon bond rotation. A conformational preference in **(112)** could then encourage π-face selective cyclisation onto the allyl cation to form the major diastereomeric product **(120a)** following rapid proton transfer as suggested previously. This mechanism differs from the first in the timing of the stereochemical induction; here the stereochemistry of the major product is determined during the cyclisation step itself. Once again, it is a simplistic interpretation and cannot readily explain the sense of induction nor the solvent and concentration effects. The two mechanisms described are by no means the only possible pathways and it is conceivable that other viable alternatives lie somewhere between these two extremes. Neither are able to account for the reduction in diastereoselectivity observed with the valine- and phenylalanine-derived substrates compared with those based on phenylglycine. Their value, merely as working hypotheses should not, however, be ignored.



(123)

Scheme 87



(88)

(103a,b) (2:1)
10%

(124)

Scheme 88

The validity of the sequences described above were briefly investigated in the form of two simple experiments (Schemes 87 and 88). The sulphonamide **(123)**, readily prepared from **(89)**, was seen an a substrate analogue which, although possessing the functionality necessary to coordinate silver(I), could not undergo subsequent cyclisation. It was hoped that combination of **(123)** with silver(I) triflate in a suitable solvent would indicate complexation of the silver electrophile with the allene portion in the form of a variation of chemical shift of the allene protons when monitored by proton NMR In d_2-CH_2Cl_2, d_6-acetone and d_6-DMSO as solvents, however, no change in the shift of the allene protons of **(123)** could be detected on addition of stoichiometric silver(I) triflate.

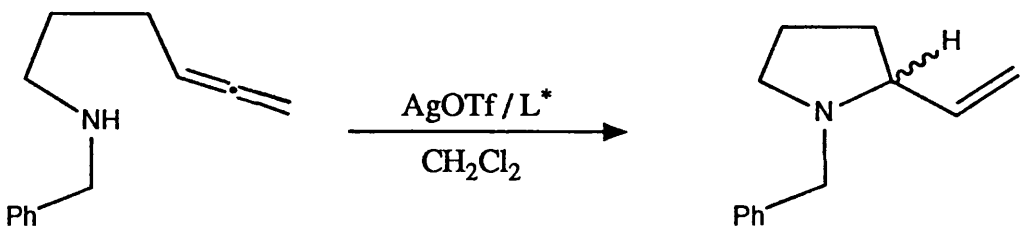
Common to both mechanistic schemes is a rapid, irreversible proton transfer to afford the vinylpyrrolidine **(120a,b)** and to release silver(I) back to the reaction medium. To probe the mode of the carbon-silver bond cleavage, the cyclisation of **(88)** was carried out in the presence of a one-electron oxidant (nitrobenzene). If the cleavage was homolytic, dimeric products of the type **(124)** might be expected. Carrying out the reaction in the presence of 1.4 equivalents of nitrobenzene no such products were detected but the monomeric cyclised products **(103a,b)** could be isolated in poor yield.

2.4(vi) Use of Chiral External Ligands with Silver(I)

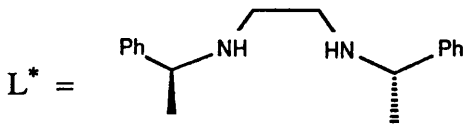
A series of experiments was carried out to investigate the degree of stereochemical control that could be achieved using a silver(I)-electrophile coordinated by chiral, non-racemic ligands.

Initially, cyclisation of the achiral *N*-benzyl amine **(125)** to the known product **(126)**[97b] was studied in terms of the enantioselectivity, using the optically active diamine **(127)**[111] as a potential bidentate ligand for the electrophile (Scheme 89).

Although the cyclisation proceeded smoothly, determination of the enantiomeric purity of the product was problematical. A procedure for the determination of the optical purity of tertiary amines by proton NMR analysis of the corresponding MTPA complex[112] proved inappropriate for this system.

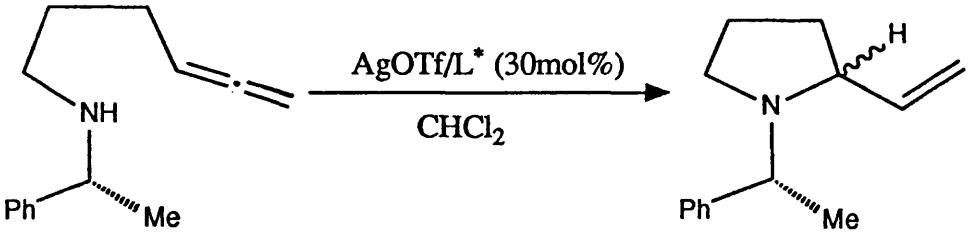


(125) **(126)**

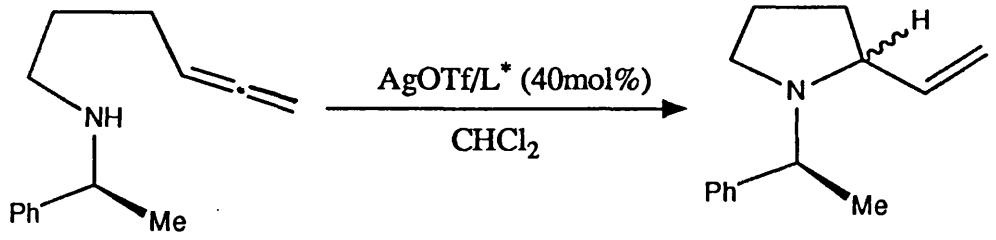


(127)

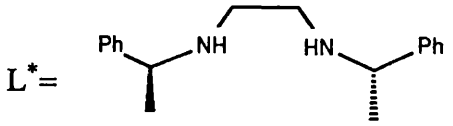
Scheme 89



(R)-(88) **(103a,b)** (2.4:1)



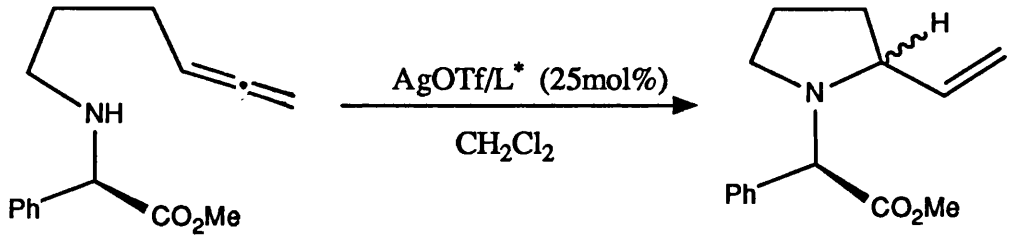
(S)-(88) **(103a,b)** (1.2:1)



(127)

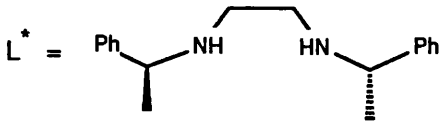
Scheme 90

It was decided to use the same chiral ligand in the silver(I)-mediated cyclisations of (S)-(**88**) and (R)-(**88**). The results are illustrated in Scheme 90 and represent a marginal influence on the diastereoselectivity; a slight increase is observed for (R)-(**88**) (ligand matched with substrate) and a slight decrease is seen for (S)-(**88**) (ligand mismatched with substrate) compared to the reaction in the absence of (**127**). Similarly, when (**89**) was employed as the cyclisation substrate in the presence of (**127**) (Scheme 91), the 2.5:1 ratio of products (**104a,b**) obtained demonstrates only a minimal change in the diastereoselectivity of the process.



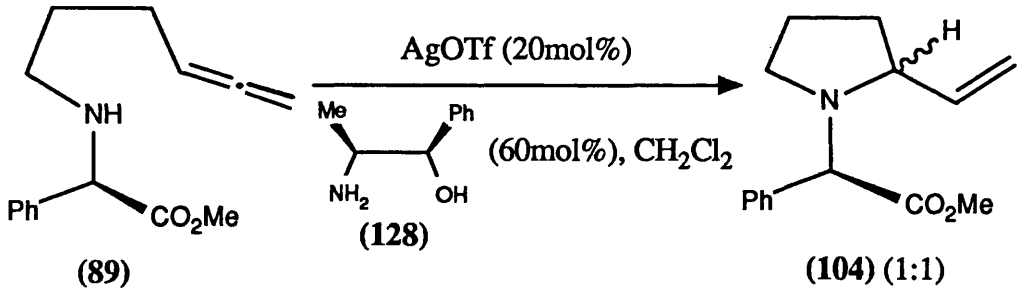
(**89**)

(**104a,b**) (2.5:1)

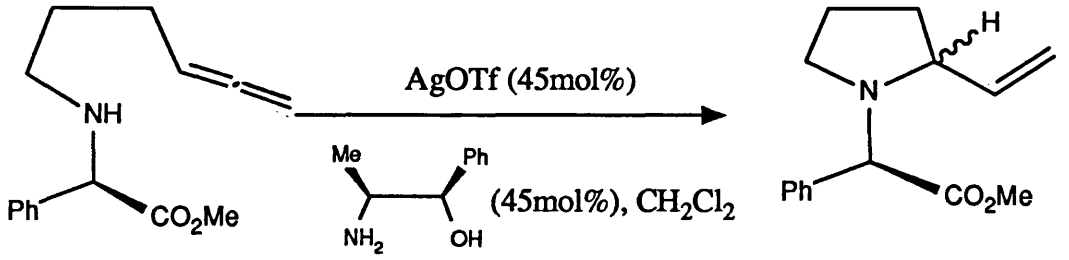


(**127**)

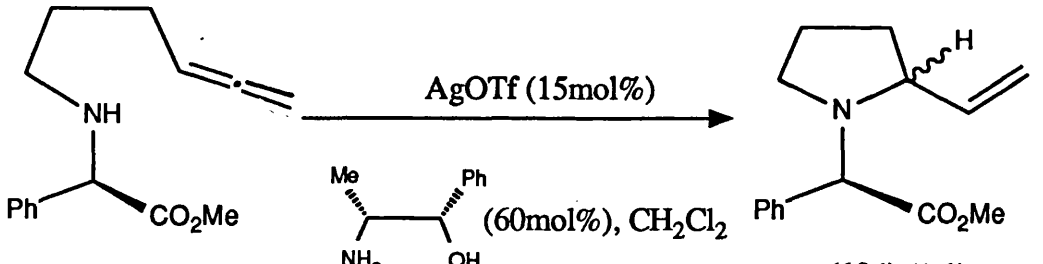
Scheme 91



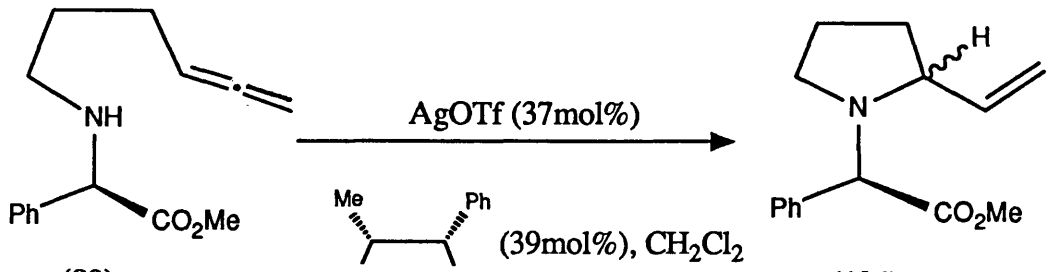
(89) **(128)** **(104)** (1:1)



(89) **(128)** **(104)** (3:1)



(89) **(129)** **(104)** (1:1)

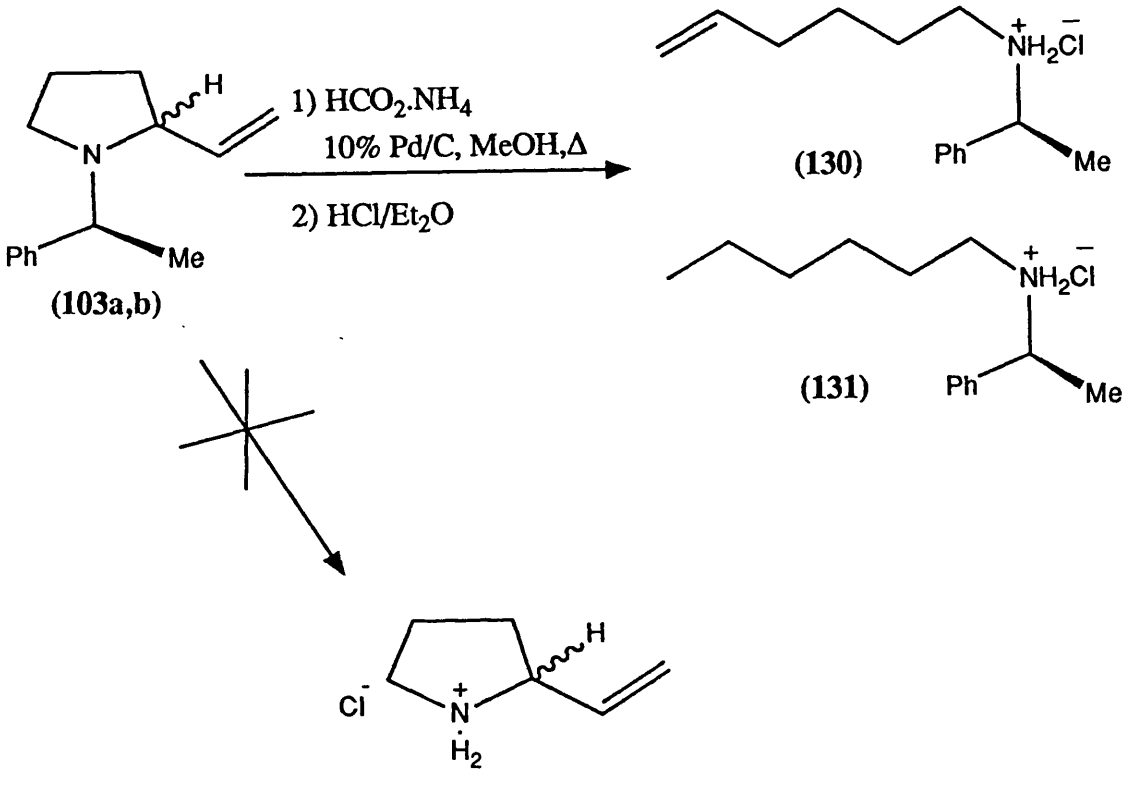


(89) **(129)** **(104)** (2.5:1)

Scheme 92

For the substrate (**89**), Scheme 92 illustrates the influence (1R, 2S)- and (1S, 2R)-norephedrine [(**128**) and (**129**)] had on the stereoselectivity of the cyclisation when present in the reaction mixture. In all cases, the presence of the ligand had a detrimental effect on the ratio of products, with no selectivity being observed when the ligand was used in a 3-4 fold excess with respect to the metal electrophile. Similarly, the use of the chiral biphosphine ligand (S,S)-CHIRAPHOS as a ligand for silver(I) in the cyclisation of the amide (**90**) had a marked influence on rate (reaction incomplete after 8 days) and resulted in reduced stereoselectivity (product ratio 4:1).

The failure of an external control element to effect stereoselectivity in an electrophile-promoted cyclisation reaction is a common problem.[113] However, the reduction in diastereoselectivity that has been observed in these processes suggests competitive coordination by the bidentate ligand to silver(I); this would interfere with the mechanism whereby stereoselectivity is induced in the absence of the ligand. Such a rationale would be in keeping with either of the two mechanistic pathways suggested earlier.



(132)-HCl

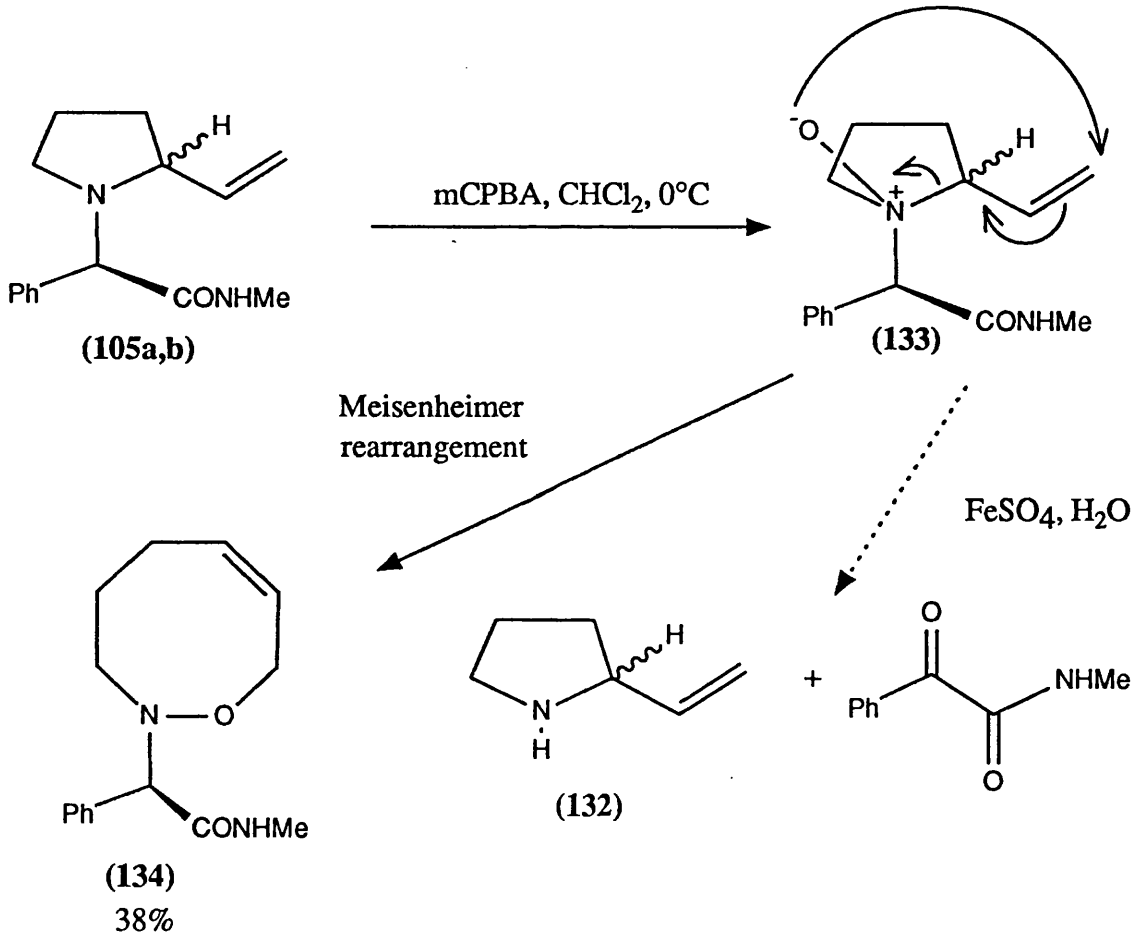
Scheme 93

2.4(vii) Approaches towards *N*-Dealkylation

Completion of the synthetic strategy aimed at the enantioselective synthesis of optically-pure functionalised pyrrolidines, outlined in Scheme 62, necessitates *N*-dealkylation to remove the control element, following cyclisation and separation. The studies carried out in this respect have focussed on the phenylglycine-based substrates since the cyclised products are obtained with the highest levels of diastereoselectivity and the *N*-benzyl subunit would be expected to encourage facile cleavage.

For the cyclised products themselves, selective hydrogenolysis of the chiral residue in the presence of the double bond of the vinyl substituent appeared to be unlikely.[114] It was hoped, however, that a catalytic transfer hydrogenolysis procedure[115] might exhibit a degree of selectivity for *N*-debenzylation. Treatment of the cyclisation product mixture **(103a,b)** with ammonium formate (4 equivalents) and 10% palladium on carbon (0.3 equivalents) in refluxing methanol[116] for 30 minutes afforded products with NMR and mass spectra suggesting the structures **(130)** and **(131)** (Scheme 93) in which *N*-dealkylation had occurred in preference to *N*-debenzylation. Rapid hydrogenolysis of tertiary allylic amines has been noted previously under similar conditions.[117]

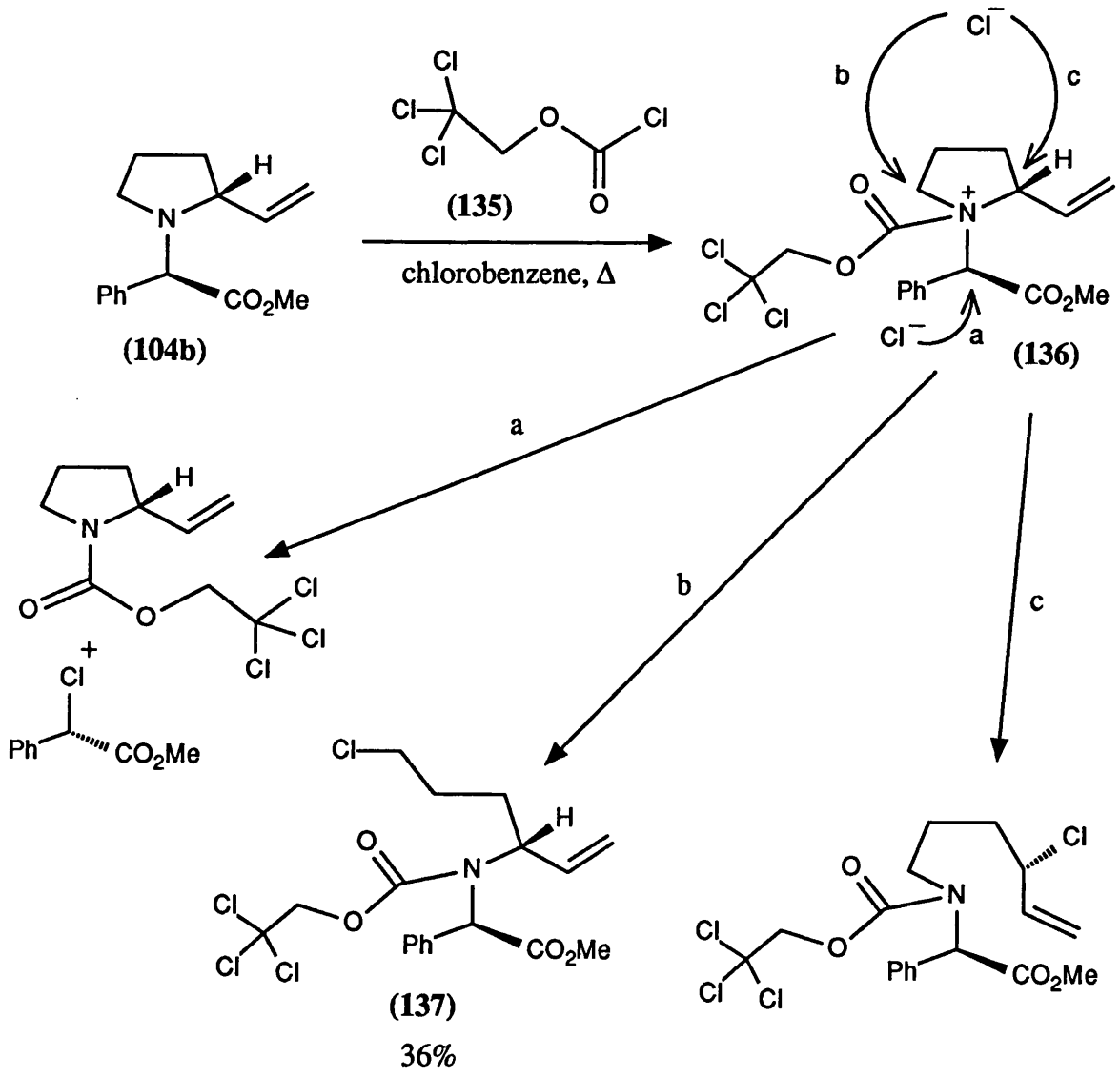
The efficient reductive cleavage of *N*-benzyl substituents in amides using lithium or sodium in liquid ammonia[118] cannot be readily applied to benzylamines[119] and for this reason, alternative methods of dealkylations were explored.


mCPBA, CHCl2, 0°C
(105a,b)
(133)
Meisenheimer
rearrangement
FeSO4, H2O
(132)
(134)
38%

Scheme 94

The conditions for oxidative removal of *N*-benzyl substituents using ceric ammonium nitrate in aqueous acetonitrile, reported by Yoshimura[120] were applied to the cyclised amide mixture **(105a,b)** but none of the desired *N*-dealkylated product could be detected in the crude reaction mixture.

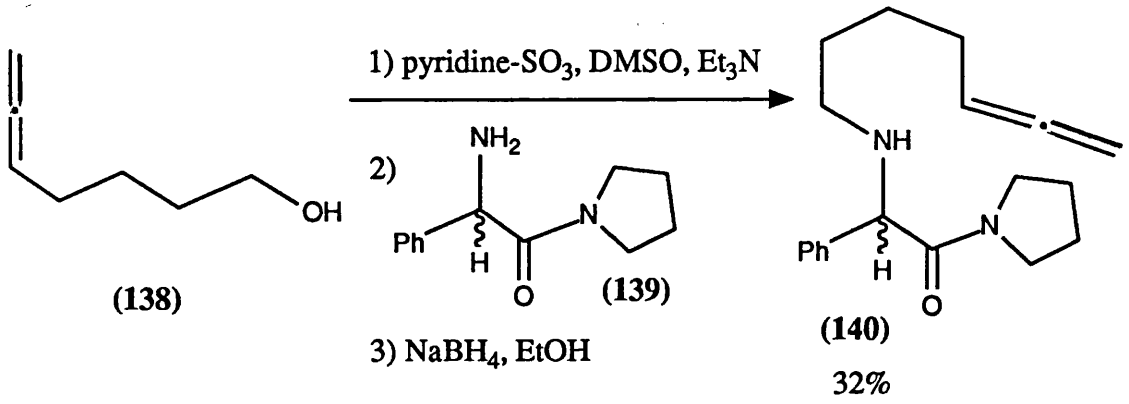
An alternative approach that was attempted was the iron(II)-catalysed dealkylation of tertiary amine oxides reported initially by Ferris[121] and later exploited by Monkovic.[122] Scheme 94 indicates the predicted route to the desired product **(132)** starting from **(105a,b)** although in practice, the major product, obtained in 38% yield, was the ring expanded eight-membered cyclic product **(134)**. Its formation may be explained by spontaneous Meisenheimer rearrangement[123] of the intermediate allylamine *N*-oxide, a process that has been well documented by Inouye.[124]



Scheme 95

The final *N*-dealkylation procedure undertaken in this system was an acylation/dealkylation sequence employing an appropriate acyl chloride.[125] Although ethyl chloroformate[126] failed to react with the minor cyclised methyl ester **(104b)** in refluxing benzene, 2,2,2-trichloroethyl chloroformate **(135)**[127] reacted cleanly. Analysis of the product suggested it was acyclic, thus ruling out chloride attack on the intermediate acylammonium cation **(136)** (Scheme 95) by the desired path a. The product was assigned as the ring-opened species **(137)** (path b) on the basis of proton NMR which indicated the downfield shift of the proton formerly at C2 of the pyrrolidine ring. This mode of reaction, where the chloride attack effects an overall ring cleavage (paths b,c) rather than an *N*-dealkylation (path a) has been described in previous work.[125]

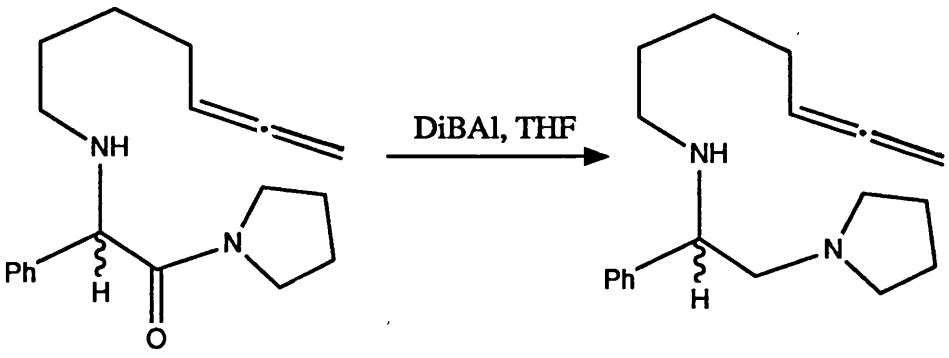
Although of the various methods attempted for *N*-dealkylation of the cyclised products, none has been successful, complications owing to the presence of the vinyl group has been a common feature. It follows that these vinylpyrrolidines are potentially amenable to *N*-debenzylation by standard means (e.g. hydrogenolysis) following functionalisation of the olefin portion. In the corresponding palladium(II)-mediated cyclisation, further chemical elaboration of the product enables clean *N*-debenzylation *via* an *N*-acylation/displacement sequence and this constitutes a key step in the synthetic approach towards the natural product target (*vide infra*). No such elaboration of the products from the silver(I)-mediated cyclisation was undertaken owing to their more limited synthetic utility.


1) pyridine-SO3, DMSO, Et3N
2)
3) NaBH4, EtOH
OH
NH2
Ph
H
O
N
NH
(138)
(139)
(140)
32%

Scheme 96

2.4(viii) Silver(I)- Mediated Cyclisation of δ-Allenic Amines.

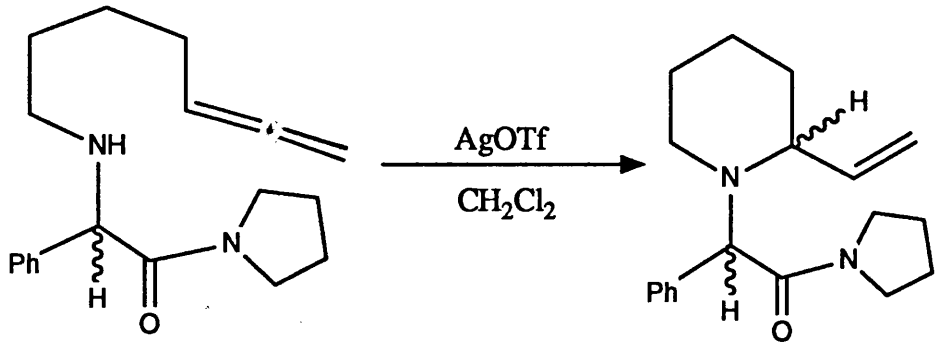
The scope of the silver(I)-mediated cyclisation of allenic amines was examined briefly in terms of the ability to synthesis six-membered ring nitrogen-containing heterocycles from the acyclic precursors **(140)** and **(141)**. The δ-allenic aminoamide **(140)** was prepared from 6,7-heptadienol **(138)**[128] using pyridine-sulphur trioxide complex in DMSO[129] (Scheme 96), followed by a reductive amination sequence employing the racemic pyrrolidine-based aminoamide **(139)**.[130] The corresponding diamine **(141)** was derived from **(140)** by reduction with DiBAl in THF (Scheme 97).



(140) **(141)**

45%

Scheme 97



(140) **(142a,b)**

Scheme 98

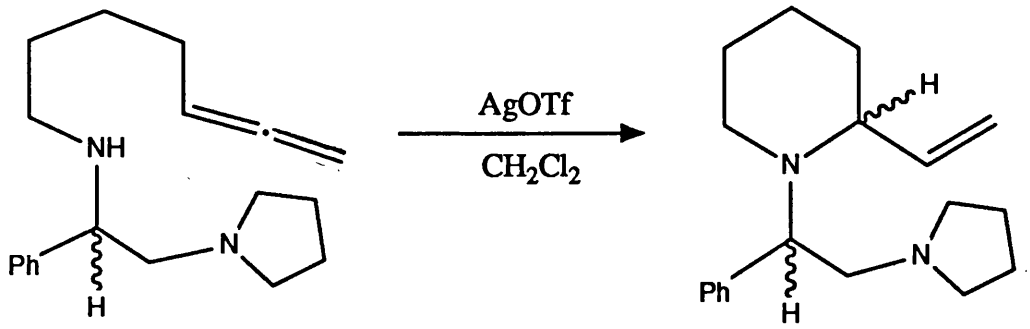
Entry	Mol% Ag(I)	142a:142b (d.e.)[1]	Reaction time	Yield
1	18%	6:1 (71%d.e.)	45h	84%
2	63%	3.7:1 (57%)	16h	62%
3	100%	7.2:1 (76%d.e.)	24h	77%

1 : Relative stereochemistry of products (a) and (b) not determined

Table 6

The results of the silver(I)-mediated cyclisations of these two substrates are indicated in Tables 6 and 7. The reactions were carried out in an analogous fashion to that described for the five-membered ring series and the products analysed as before.

The results for the cyclisation of the substrate **(140)** highlight a number of observations. Firstly, the kinetic preference for the formation of five-membered rings compared with six is indicated by the reaction times which are a factor of ten times greater than those for the substrate **(90)**. Secondly, a variation of diastereoselectivity in the formation of **(142a,b)** with molar proportion of silver(I)-electrophile is once again seen, although a lower selectivity is obtained using 63 mol% compared with either 18 mol% or 100 mol%. This is the opposite trend to that seen in the five-membered ring series. Finally, the levels of diastereoselectivity, although slightly lower than those for the cyclisation of **(90)** are comparable. This contrasts with the poor selectivity (d.e.< 50%) seen in the cyclisation of the pyrrolidine-derived amino amide in the five-membered ring series.[130]



(141) **(143a,b)**

Scheme 99

Entry	Mol% Ag(I)	143a:143b[1] (d.e.)	Reaction time	Yield
1	13%	No reaction after 6 days		
2	56%	1.1:1 (5%d.e.)	6 days	50% conversion
3	84%	No significant reaction after 30h		
4	160%	2.3:1 (39%d.e.)	52h	87%

1 : Relative stereochemistry of products **(a)** and **(b)** not determined

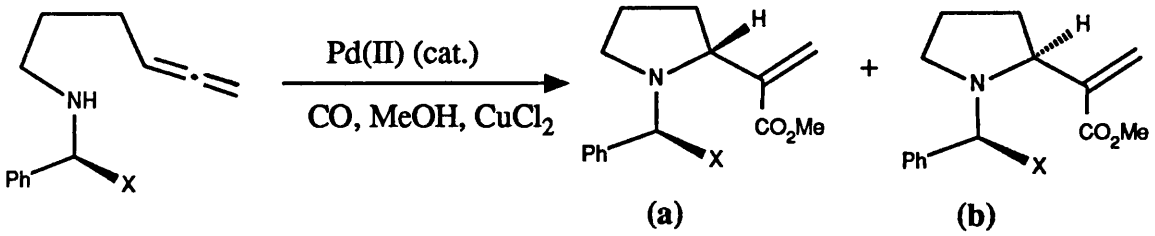
Table 7

Table 7 indicates that the diamine **(141)** is a poor substrate for silver(I)-mediated cyclisation and complete reaction is achieved only in the presence of excess silver(I)-electrophile (entry 4) with a low level of selectivity. When approximately 50 mol% of electrophile is used (entry 2) the reaction proceeds with only 50% conversion and this suggests that the metal ion is being "complexed-out" in preference to mediating the six-membered ring formation. It appears, therefore, that these two substrates delineate both the scope and limitations of the silver(I)-mediated cyclisation. Depending on the particular control element used, the cyclisation may proceed cleanly in good yield and with high diastereoselectivity or, as in the case of **(141)**, cyclisation proceeds with difficulty and exhibits poor levels of stereochemical control.

Inherent to all the silver(I)-mediated cyclisations discussed in this chapter is the limited synthetic potential of the vinyl group in the cyclised product. The next section explores the diastereoselectivity available in a cyclisation process which affords products amenable to a much wider range of chemical manipulation.

2.5 The Palladium (II)-Mediated Cyclisation

2.5(i) The cyclisation of the allenic amine substrates to afford products of the type **(84)** (Scheme 66, X = CO_2Me) was carried out using catalytic quantities of an appropriate palladium(II) salt under carbomethoxylation conditions.[96b] The presence of stoichiometric copper(II) chloride in the reaction mixture (typically 3 equivalents) effected reoxidation of the palladium electrophile.[131] A variety of palladium(II) salts were used in an attempt to influence the diastereoselectivity of the cyclisations and where necessary, these were conveniently prepared by standard literature methods.[132] The reactions were carried out at room temperature and once complete, the metal salts were removed by an aqueous ethanolamine wash. The diastereoselectivity of the transformations was determined as in the silver(I)-mediated cyclisation, by proton NMR analysis of the reaction mixture. Where necessary, further purification was once again achieved by silica gel chromatography. The results are presented in Tables 8 and 9, illustrating the success of the process in terms of the yield of cyclised products and the distribution of diastereoisomers.



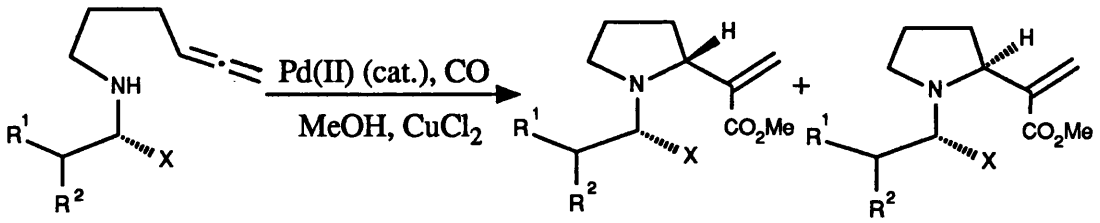
Scheme 100

Entry	Allenic amine	Products	Catalyst (mol%)	(a):(b)[1] (d.e.)	Yield
1	(88)	(144a,b)	$PdCl_2$ (4%)	1.1:1 (5%d.e.)	82%
2	(88)	(144a,b)	$Pd(PPh_3)_2Cl_2$ (2%)	1.1:1 (5%d.e.)	87%
3	(89)	(145a,b)	$Pd(PhCN)_2Cl_2$ (20%)	2.5:1 (43%d.e.)	71%
4	(89)	(145a,b)	$Pd(OAc)_2$ (10%)	2:1 (33%d.e.)	n.d.
5	(90)	(146a,b)	$Pd(PhCN)_2Cl_2$ (16%)	1.7:1 (26%d.e.)	74%
6	(96)	(147a,b)	$Pd(PhCN)_2Cl_2$ (22%)	1:1 (0%d.e.)	44%

1 : With the exception of entries 1 and 2 the assignment of relative stereochemostry for products (a) and (b) is purely arbitrary.

n.d. : yield not determined

Table 8



(a) (b)

R^1 = Ph, R^2 = H ; phenylalanine-based derivatives

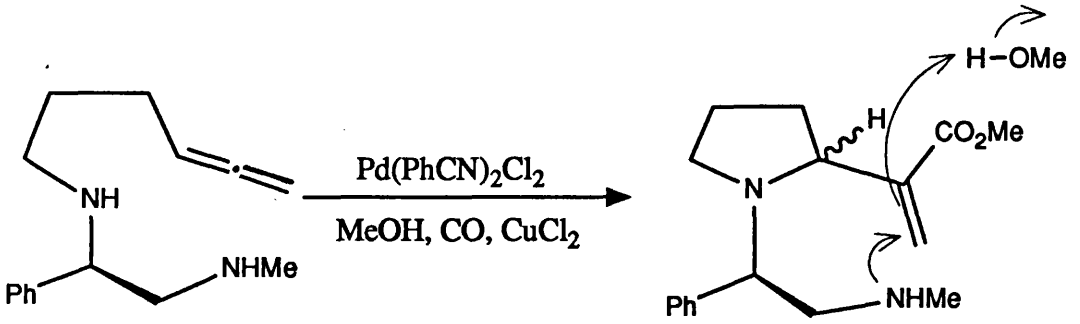
R^1 = R^2 = Me ; valine-based derivatives

Scheme 101

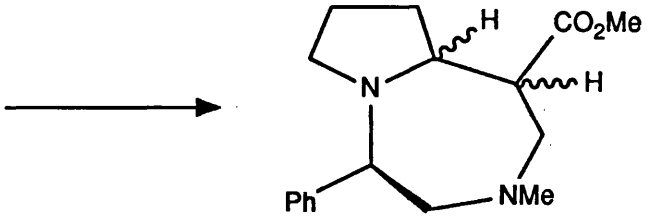
Entry	Allenic amine	Products	Catalyst (mol%)	(a):(b)[1] (d.e.)	Yield
1	(91)	(148a,b)	$PdCl_2$ (50%)	1.2:1 (9%d.e.)	98%
2	(91)	(148a,b)	$Pd(PPh_3)_2Cl_2$ (10%)	1.6:1 (23%d.e.)	90%
3	(91)	(148a,b)	$Pd(PhCN)_2Cl_2$ (17%)	1.3:1 (13%d.e.)	71%
4	(92)	(149a,b)	$PdCl_2$ (13%)	1:1 (0%d.e.)	58%
5	(93)	(150a,b)	$Pd(PhCN)_2Cl_2$ (15%)	1.9:1 (31%d.e.)	59%
6	(97)	(151a,b)	$PdCl_2$ (10%)	1.4:1 (17%d.e.)	33%

1 : The assignment of relative stereochemistry of products (a) and (b) is purely arbitrary.

Table 9



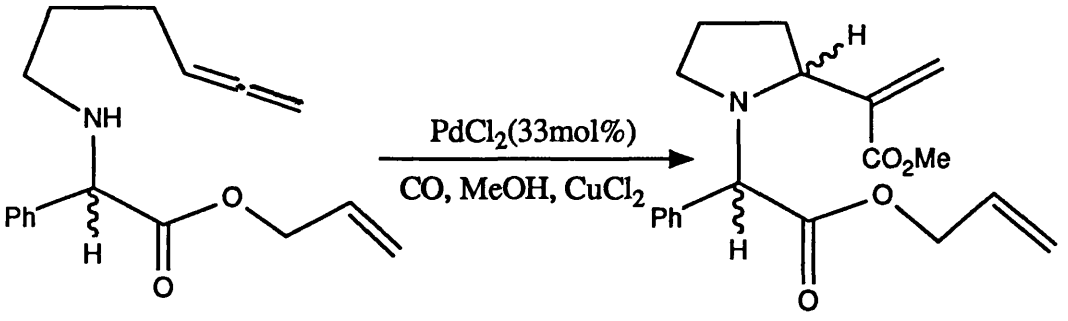
(100) **(152a,b)**



(153a-d)

48%

Scheme 102



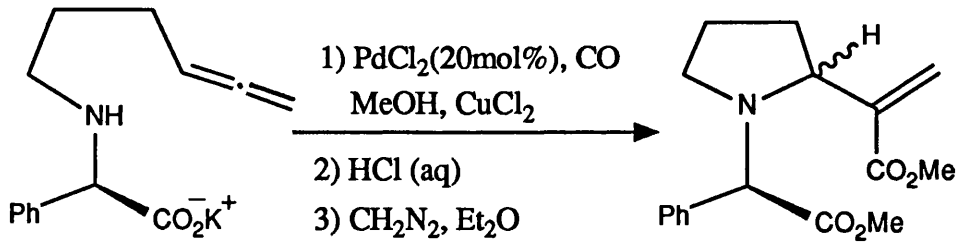
(102) **(154a,b)** (1:1)

18%

Scheme 103

Analysis of the palladium(II)-mediated cyclisation of the phenylglycine-derived diamine **(100)** was complicated by 1,4 addition of the *N*-methylamino group to the newly-formed acrylate function in **(152a,b)** (Scheme 102). The resulting mixture of four diastereomeric bicyclic products **(153a-d)** included two major components in a ratio of 3:2, the major being fully characterised. Cyclisation of the allyl ester **(102)** (Scheme 103) introduced difficulties resulting from transesterification under the reaction conditions. Thus, the cyclised product **(154a,b)** was obtained in poor yield and in a ratio reflecting an absence of diastereoselectivity in the transformation.

The carboxylate salt **(101)** was subjected to the palladium(II)-mediated cyclisation/carbomethoxylation conditions (Scheme 104). Following protonation of the product and subsequent methylation, the proton NMR spectrum of the crude reaction mixture indicated a 3:2 ratio of desired cyclised methyl esters **(145a,b)**.

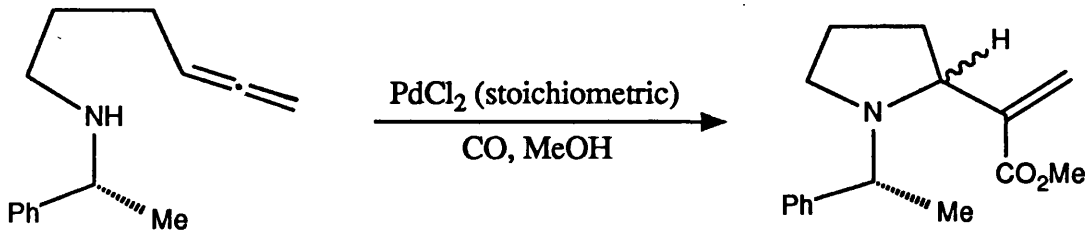


(101) **(145a,b)** (3:2)

Scheme 104

Although the products of cyclisation with the remaining substrates are obtained often in high chemical yields, the stereoselectivity displayed by this process is rather less impressive. The cyclisations of the methyl esters **(89)**, **(91)** and **(93)** proceed with a moderate degree of selectivity but the levels of discrimination are uniformly lower than in the corresponding silver(I)-mediated process. Moreover, no analogous pattern of product distribution, as the control element group X is varied, can be discerned and the choice of palladium(II) complex had minimal influence on the stereochemical outcome.

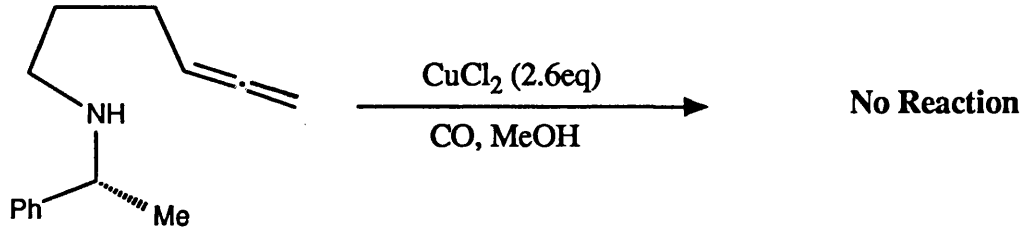
Such observations lead to the conclusion that this transformation proceeds by an alternative mechanistic pathway to either of those suggested for the silver(I)-mediated process. Before discussing the proposed sequence (Section 2.5 (iii)) a number of control experiments were carried out which support the favoured mechanism whilst eliminating a number of other possibilities and these are described briefly in the next section.



R-(88)

(144a,b) (1:1)
27%

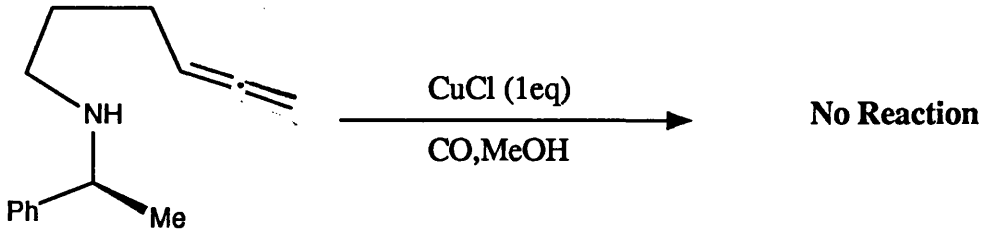
Scheme 105



No Reaction

R-(88)

Scheme 106



No Reaction

S-(88)

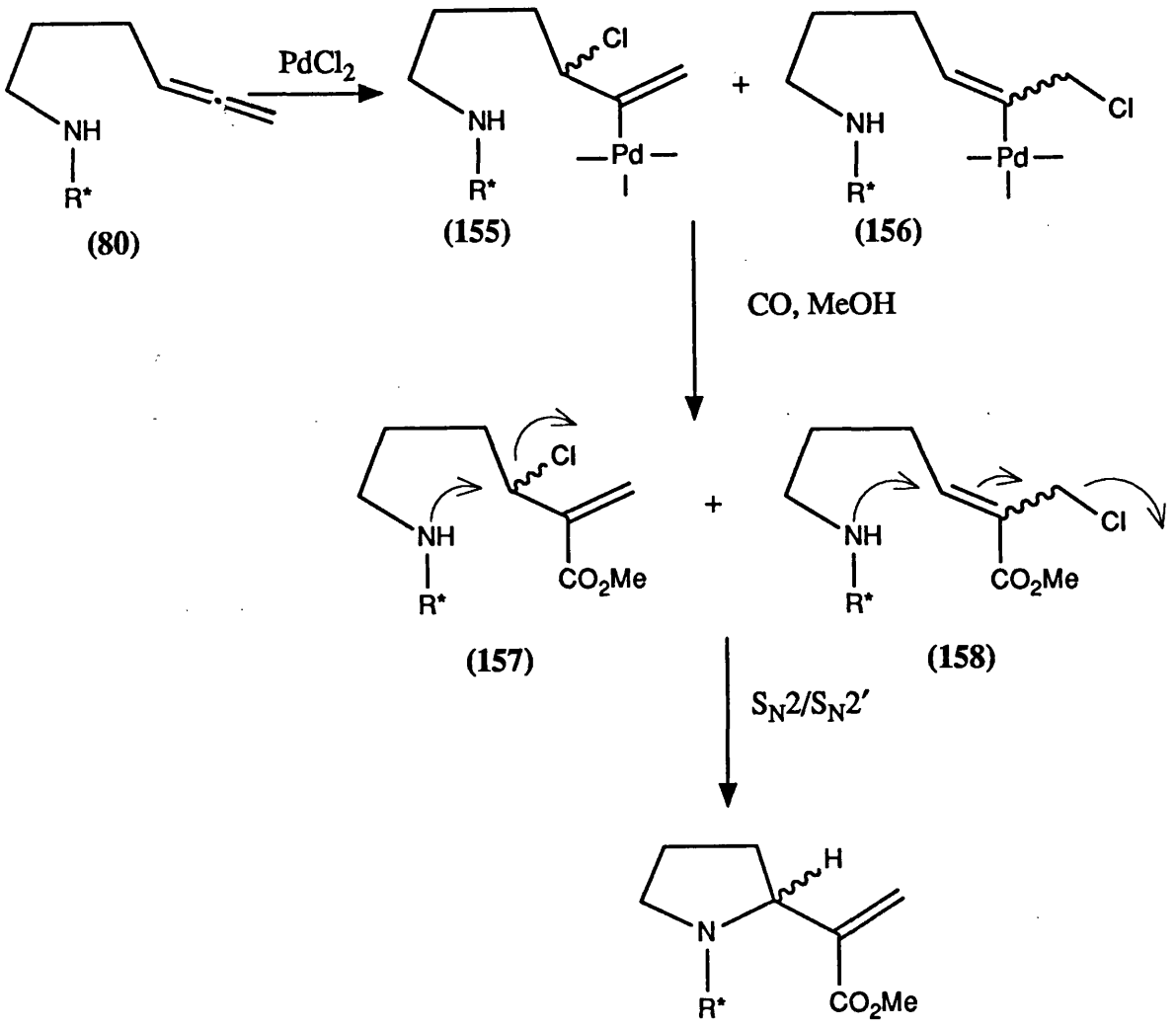
Scheme 107

2.5(ii) Control Experiments

As a means of establishing that palladium(II) is, in fact, the active electrophilic species in these transformations, a reaction was carried out employing a stoichiometric quantity of palladium(II) chloride in the absence of copper(II) chloride (Scheme 105). Cyclisation of (R)-(**88**) proceeded to completion within 1h to afford the acrylate esters (**144**) in a 1:1 ratio and a yield of 27% that reflected the difficulty in removing precipitated palladium(0).

To investigate the role of copper(II) in the carbomethoxylation cyclisation, the same substrate (R)-(**88**) was subjected to the usual reaction conditions, with the omission of palladium(II) chloride (Scheme 106). After 24h at room temperature, no reaction was observed and this dismissed the possibility of any participation of copper(II) chloride in the cyclisation other than as a reoxidant for palladium.

In oxidising palladium(0) to the active palladium(II), copper(II) is itself reduced to copper(I). It was necessary, therefore, to carry out a similar control experiment with copper(I) chloride (Scheme 107). In the presence of stoichiometric copper(I) under carbomethoxylation conditions at room temperature, (S)-(**88**) underwent no significant conversion after 12h and this confirmed palladium(II) as the only active electrophilic species in the cyclisation reactions discussed in this study. An enlightening and valuable observation was that the combination of copper(I) chloride and allenic amine substrates, in either dichloromethane or refluxing methanol, does result in the formation of mixtures of dimeric cyclised products. This aspect of the role of copper(I) as an active electrophile is discussed more fully in section 2.6.



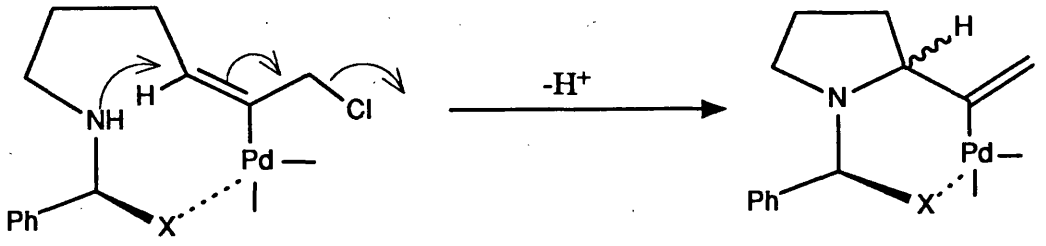
(80) (155) (156) (157) (158) (159)

Scheme 108

2.5(iii) Proposed Mechanism for the Palladium(II)-Mediated Cyclisation

Based on the work of Schultz[86a] and Shaw[86b] discussed in Section 1.3 (Scheme 52) in which allene was observed to undergo *syn*-chloropalladation when combined with palladium(II) chloride, the following mechanism is proposed for the palladium(II)-mediated cyclisations of the allenic amine substrates (Scheme 108).

Initial *syn*-chloropalladation of the allene portion in **(80)** may occur across the internal double bond to give **(155)** or across the terminal π-system to afford **(156)**. Neither of these processes would be expected to proceed with stereochemical control by the stereogenic residue R^* since it is too remote from the reacting centre. Hence **(155)** is formed as a mixture of diastereoisomers and **(156)**, more specifically, as a mixture of double bond geometrical isomers. Carbonyl insertion into the vinyl-palladium bond followed by nucleophilic attack of the acylpalladium intermediate by methanol[133] affords the mixture of acyclic acrylate esters **(157)** and **(158)**. Cyclisation of **(157)** by backside displacement of chloride with inversion results in the formation of the product **(159)** with stereoselectivity reflecting the face selectivity of the initial *syn*-chloropalladation process. Cyclisation of **(158)** by an S_N2' mechanism would not be expected to be under any significant degree of stereochemical control.



(160) **(161)**

Scheme 109

Crucial to this mechanistic interpretation is that the carbomethoxylation of **(156)** occurs more rapidly than S_N2'-cyclisation. Were this not the case, cyclisation of **(160)** (Scheme 109), where X is able to coordinate palladium, might be expected to exhibit stereoselectivity in the product **(161)** owing to the type of conformational bias suggested for one of the proposed silver(I)-mediated reaction mechanisms (Scheme 86). Experimental evidence for the carbomethoxylation occurring more rapidly than cyclisation of such intermediates will be discussed in section 2.6(iii).

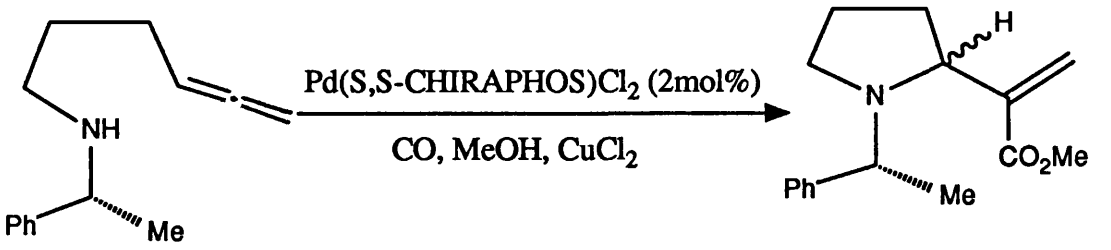
Within the context of the development of methodology for the enantioselective formation of optically pure functionalised vinylpyrrolidines, the palladium(II)-mediated process offers a number of notable features. The products of the reaction are valuable synthetic building-blocks, the diastereoisomers are, in general, readily separable and, in the case of the products of cyclisation of **(88)**, facile *N*-debenzylation has proved to be a valuable property of this system (*vide infra*).

The obvious disadvantage that emerges from the study is the low level of diastereoselectivity achieved and it was determined to attempt various approaches to improve this aspect of the reaction. The next two sections deal with the efforts carried out in this respect.

2.5(iv) Use of Chiral Ligands on Palladium(II)

According to the proposed mechanism of palladium(II)-mediated cyclisation, non-stereoselective addition of palladium(II) chloride to the allene π-system is a major factor responsible for the poor diastereoselectivities observed in the products. It was hoped that attachment of appropriate chiral bidentate ligands to the palladium electrophile would induce asymmetry during this initial step. The difficulty in effecting asymmetric electrophile-promoted cyclisations by attaching chiral ligands to the electrophilic species has already been alluded to.[113] There are, however, examples where such an approach has resulted in enantioselectivities of up to 73% e.e. with rhodium(I)-based systems.[134] Three optically pure ligands were investigated: (S,S)-CHIRAPHOS,[135] (R)-BINAP[136] and (+)-diethyl tartrate, the latter being selected in the light of its use in asymmetric carbonylations of prochiral olefins.[34] The results are illustrated as Schemes 110-116.

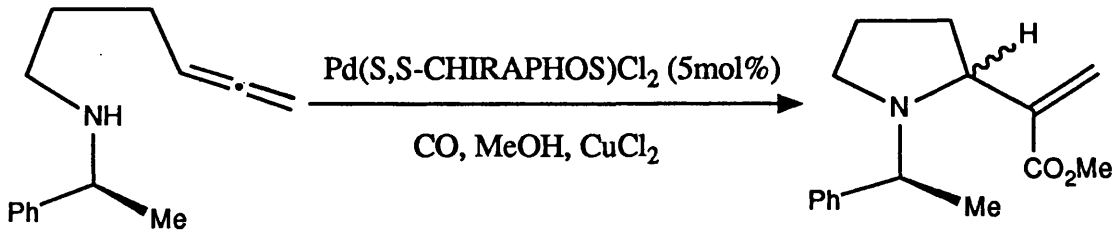
The presence of the biphosphine ligands in the reaction mixture had a profound effect on the rate of conversion, with the overall reaction times being increased by factors as much as 10-fold. When the diamine **(100)** was employed as the substrate, no cyclised product formation was detected after 24h.



R-(88)

(144a,b) (1:1)

82%

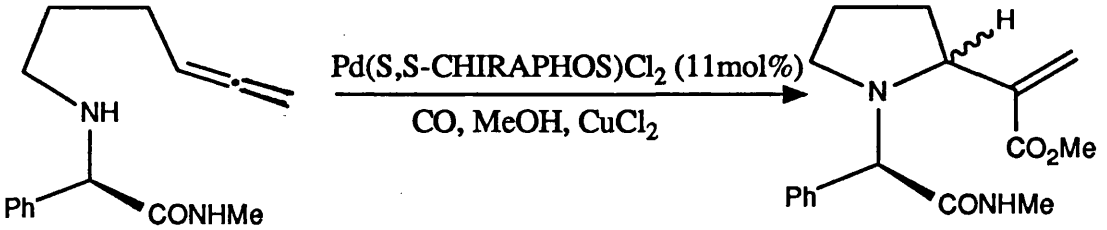


S-(88)

(144a,b) (1:1)

82%

Scheme 110

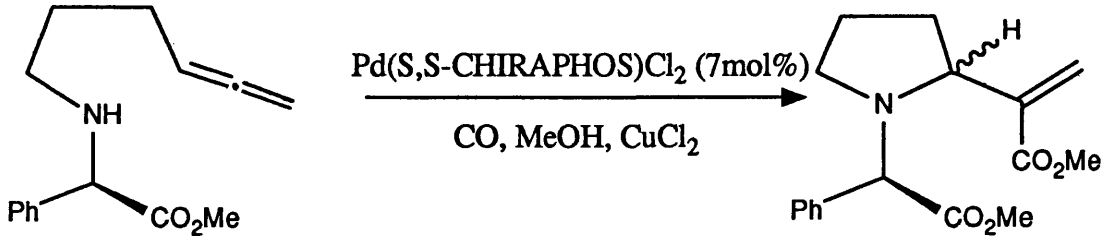


(90)

(146a,b) (1.6:1)

92%

Scheme 111



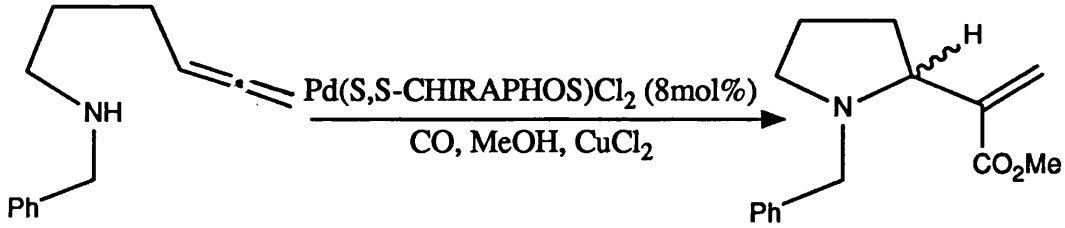
(89)

(145) (2:1)

77%

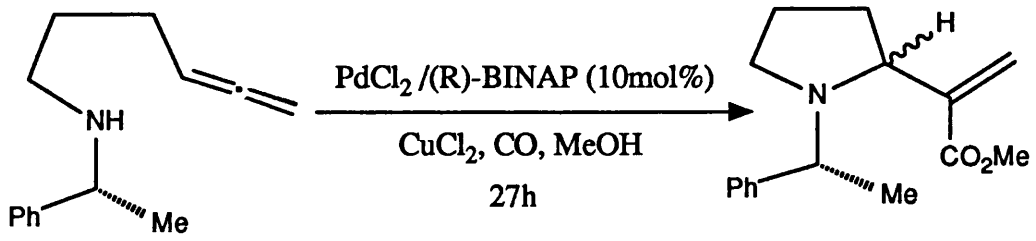
Scheme 112

Schemes 110-112 indicate the minimal effect of (S,S)-CHIRAPHOS on diastereoselectivity employing as substrates the α-methylbenzyl derivatives (R)- and (S)-(**88**), the amide (**90**) and the methyl ester (**89**). Cyclisation of the achiral substrate (**125**) (Scheme 113) afforded the corresponding acrylate ester product (**162**) in good yield.[96b] However, determination of the e.e. of this product by the method of Villani[112] indicated an enantiomeric ratio of 1:1 by comparison of the integrals for the split singlet corresponding to the ester methyl signal in the amine/(R)-MTPA proton NMR spectrum.



(**125**) (**162**)
83%
enantiomeric ratio 1:1

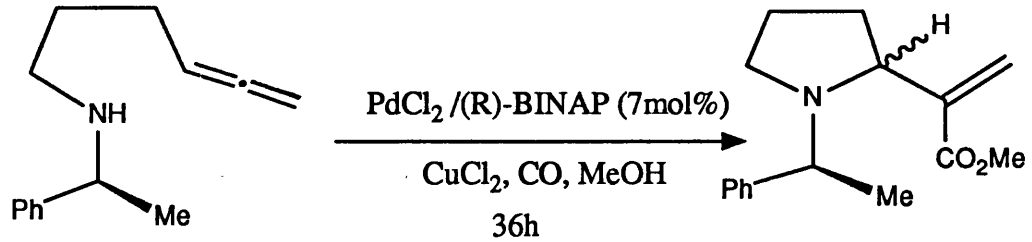
Scheme 113



R-(88)

(144a,b) (1:1)

50% conversion

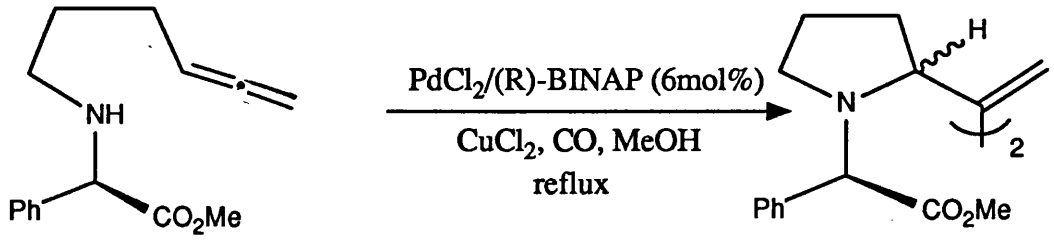


S-(88)

(144a,b) (1:1)

30% conversion

Scheme 114



(89)

(163)

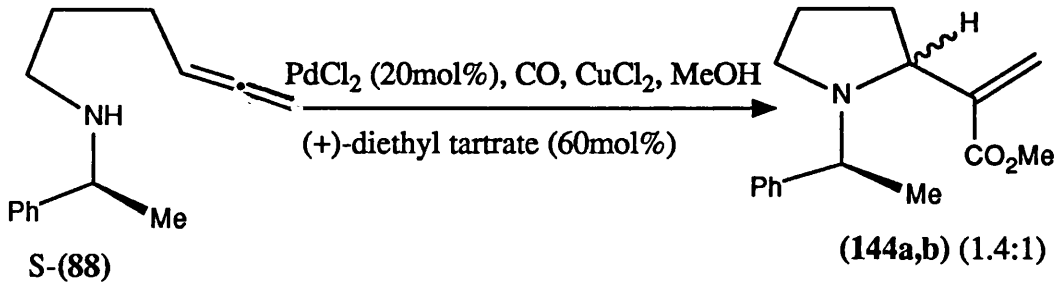
14%

Scheme 115

Similarly, the use of (R)-BINAP as a chiral ligand (Scheme 114) effected no observable diastereoselectivity in the cyclisation of (R)- or (S)-(**88**), merely an increase in reaction time.

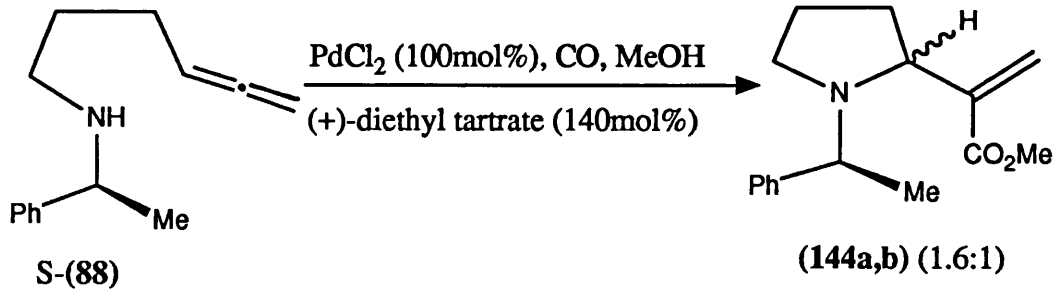
For the methyl ester (**89**), no reaction was observed after 6h at room temperature, employing 6 mol% of both catalyst and ligand. On refluxing for 30 min., however, complete disappearance of the substrate led to a product mixture comprising a small amount of required (**104a,b**) in a ratio of (1:1) along with a mixture of cyclised dimers (**163**), the major component of which was fully characterised.

These results suggest that the steric bulk imparted to the palladium complex by the phosphine ligands has a detrimental influence on its effectiveness as an electrophile, resulting in extended reaction times. The dimeric products (**163**) obtained from (**89**) could be the result of a coupling process involving the vinylpalladium intermediate. This would be contingent on carbonyl insertion into the vinyl-palladium bond being sufficiently disfavoured by the steric bulk of the system. An alternative and more likely scenario invokes a coupling reaction mediated by small amounts of copper(I) species present in the reaction mixture. Similar products have been isolated when stoichiometric copper(I) chloride is employed as the electrophile for transformations carried out in refluxing methanol (Section 2.6(i)).



S-(88)

(144a,b) (1.4:1)

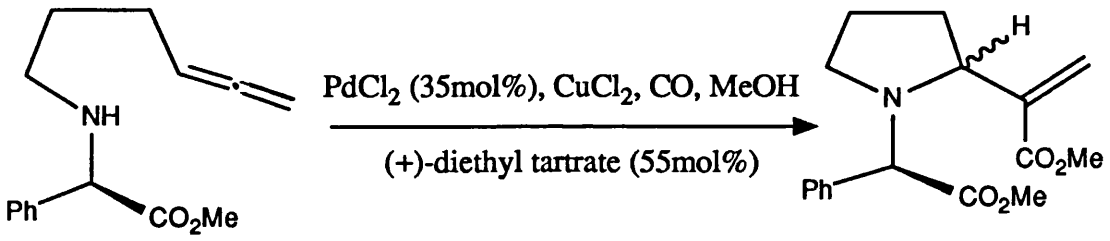


S-(88)

(144a,b) (1.6:1)

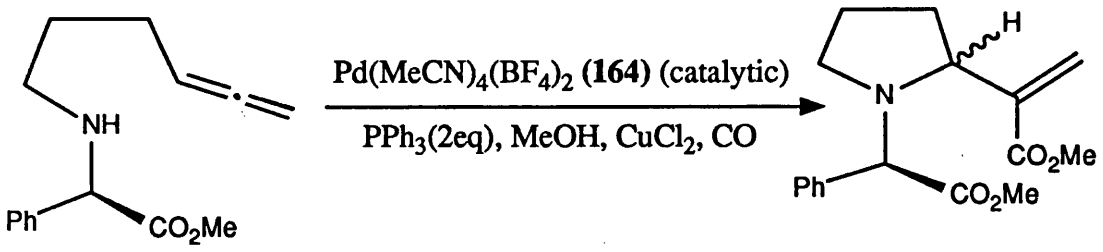
Scheme 116

The experiments with (+)-diethyl tartrate (Scheme 116) indicate a marginal influence on the diastereoselectivity of cyclisation of (S)-(**88**). The use of stoichiometric palladium(II) chloride in one example was an effort to circumvent possible preferential coordination by the amine to copper(I) or copper(II) species. This modification promoted only a small increase in diastereoselectivity. The cyclisation of the ester (**89**) once again exhibited no improvement in diastereomeric ratio in the presence of diethyl tartrate.



(89) **(145a,b)** (2.1:1)

Scheme 116 contd.



(89)

(145a,b) (1:1)
67%

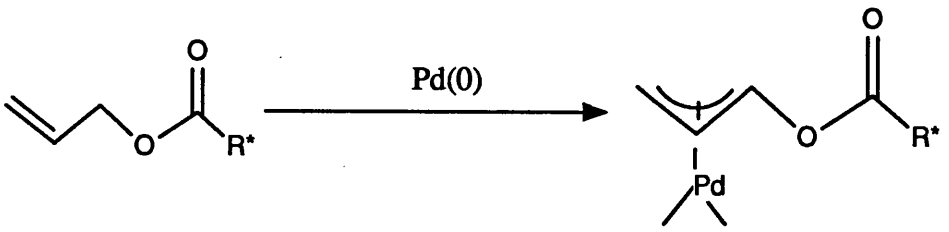
Scheme 117

2.5(v) Modification of the Palladium Electrophile

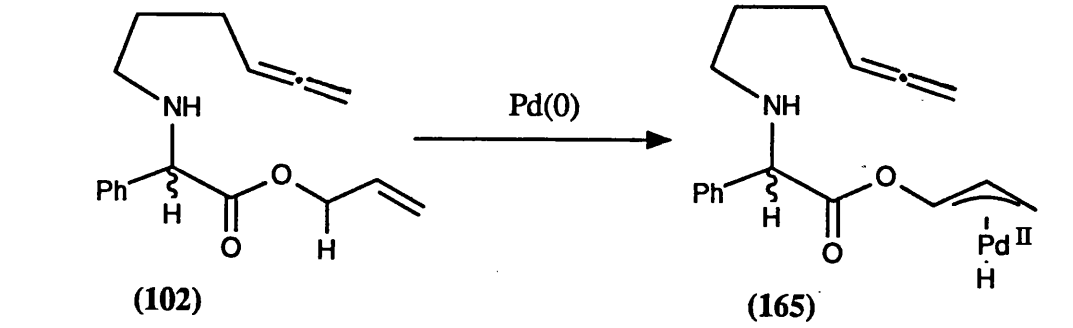
The results presented in the previous section lead to the conclusion that a diastereoface selective *syn*-chloropalladation process cannot be readily achieved simply by attaching chiral ligands to the electrophile. This section describes two attempts to effect stereoselectivity in the palladium(II)-mediated cyclisation by modifying the reaction mechanism.

The complex tetrakis(acetonitrile)palladium(II) bis(tetrafluoroborate) **(164)** differs from the palladium(II) chloride-based ligands in that this contains a non-nucleophilic counter ion. It was hoped that such a property might preclude the proposed *syn*-chloropalladation process and result in more highly face selective interactions with the allenic amines. Indeed, this complex has been used by Hegedus[137] in systems requiring a highly electrophilic palladium(II) source to effect reaction and by Sen,[138] in which evidence for the formation of incipient carbonium ions as intermediates is reported.

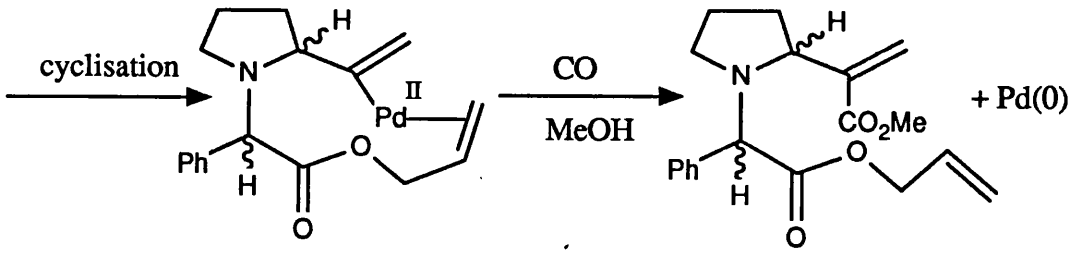
The complex was synthesised in poor yield according to the procedure of Wayland[139] and used in the cyclisation of the amino ester **(89)** (Scheme 117); in this reaction, complete loss of diastereoselectivity was observed. The presence of 2 equivalents of triphenylphosphine was necessary to maintain the catalytic activity of the electrophile.[140]



Scheme 118



(102) **(165)**

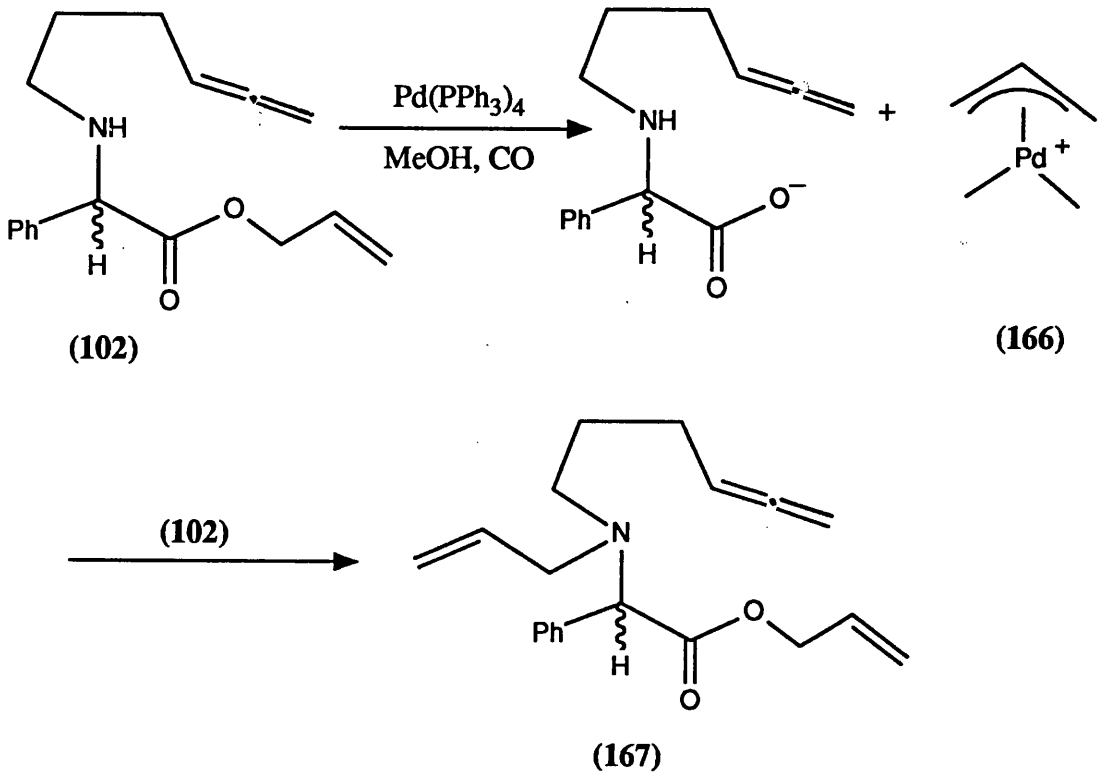


(154a,b)

Scheme 119

In 1986, Hiroi reported the use of chiral allyl esters in palladium-catalysed asymmetric allylations.[141] High optical yields were thought to be the result of initial insertion of the palladium catalyst into the C-H bond of the allyl group (Scheme 118) prior to allylation. Based on this precedent, the allyl ester **(102)** was combined with tetrakis(triphenylphosphine)palladium(0) with the intention of inducing a similar type of insertion process (Scheme 119).

The resultant π-allyl palladium species, incorporating palladium in the +2 oxidation state, would now be able to activate the allene π-system and effect cyclisation. The neighbouring asymmetric centre would be expected to effect selective delivery of the palladium(II) species onto one of the two available diastereotopic faces of the allene π-system in **(165)**. Subsequent carbomethoxylation would then regenerate the palladium(0) catalyst along with the product **(154a,b)**.



Scheme 120

In the event, combination of **(102)** with the palladium(0) complex[132] (5 mol%) in methanol effected carboxylate displacement to afford the intermediate π-allyl palladium species **(166)** which was trapped by unreacted **(102)** to afford the tertiary amine product **(167)** as the major isolable component in 12% yield (Scheme 120).

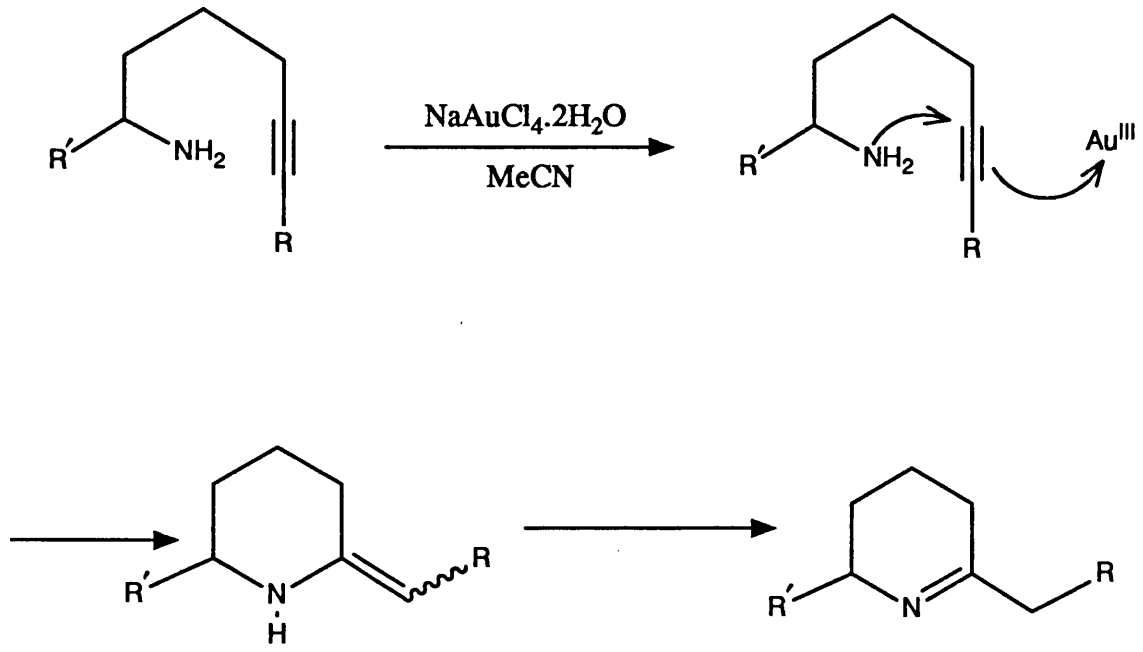
It followed from the cyclisation studies carried out using palladium-based reagents that although in many cases the desired functionalised cyclic products could be obtained, high levels of diastereoselectivity could not be achieved.

The following section discusses the use of alternative metal electrophiles which were hoped to react *via* mechanistic pathways similar to those proposed for the silver(I)-mediated cyclisation, but which lead to intermediates which could either be isolated or functionalised *in situ*. The intention, therefore, was to develop a process that would offer access to products with the required functionality and improved levels of diastereoselectivity.

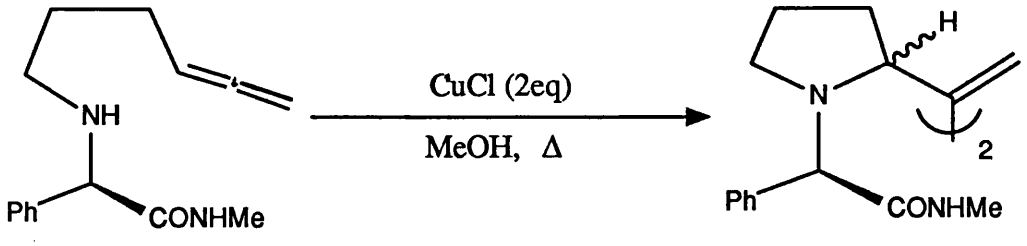
2.6 Use of Alternative Metal Electrophiles

2.6(i) Gold(III) and Copper(I) as Electrophiles

In searching for suitable alternatives to silver(I) as an electrophilic trigger for the cyclisation of allenic amines, it seemed reasonable to consider the two remaining group 1B transition metals. The use of catalytic gold(III) to promote the cyclisation of 5-alkynylamines to 2,3,4,5-tetrahydropyridines (Scheme121) has been reported by Utimoto.[142] However, when similar conditions were applied to the allenic amine substrate **(80)**, in a variety of solvents (acetonitrile, acetone, dichloromethane) no reaction was observed.

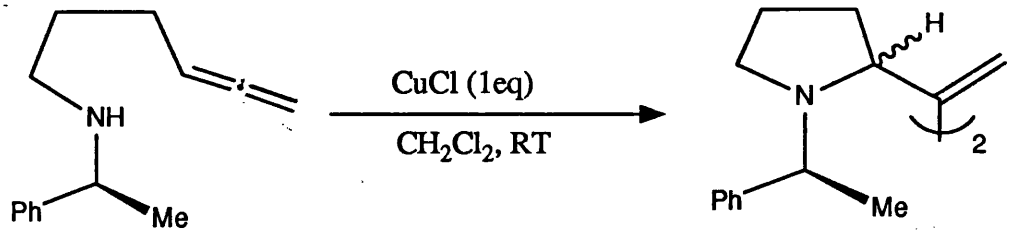


Scheme 121



(90) **(168)**

Scheme 122



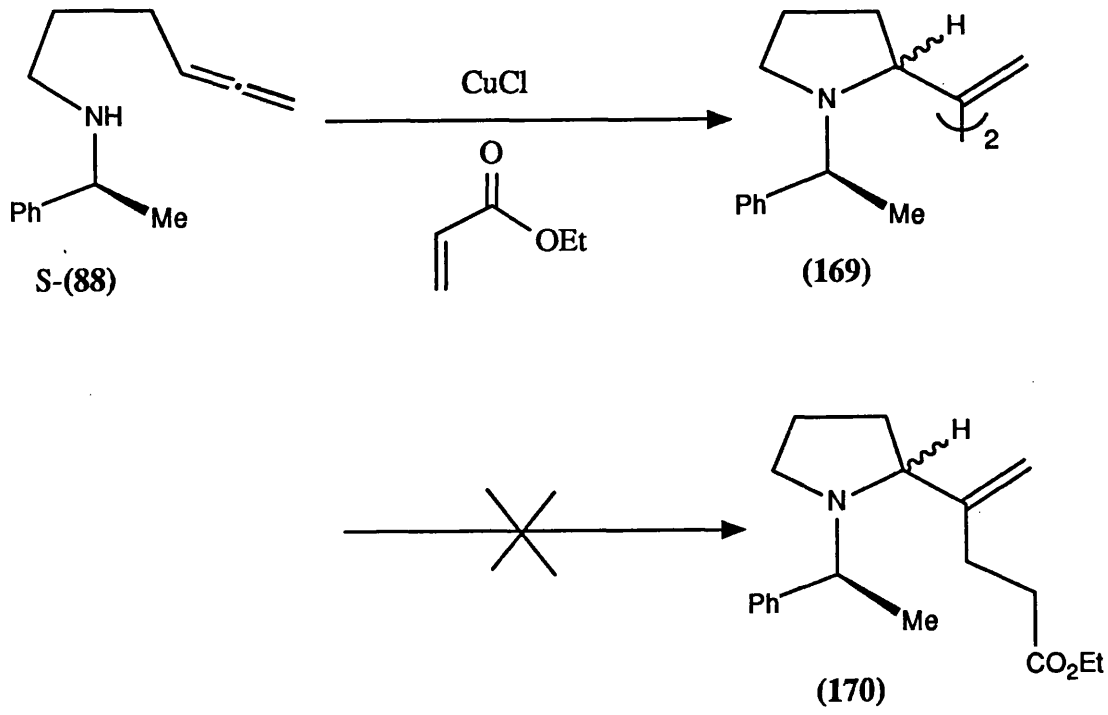
S-(88) **(169)**

Scheme 123

The brief studies carried out using copper(I) as the electrophile, although essentially an extension of the control experiments described in section 2.5(ii), proved to be more successful. The substrates **(88)** and **(90)** were resistant to copper(I)-mediated cyclisation in methanol over a period of 12h at room temperature. When, however, **(90)** was heated to reflux in methanol in the presence of 2 equivalents of copper(I) chloride, complete conversion to the dimeric species **(168)**, as a mixture of three diastereoisomers, was observed within 3h (Scheme 122). The structural assignment of **(168)** was based on the proton NMR and IR spectra of the product mixture and confirmed by the presence of a molecular ion peak in the C.I. mass spectrum.

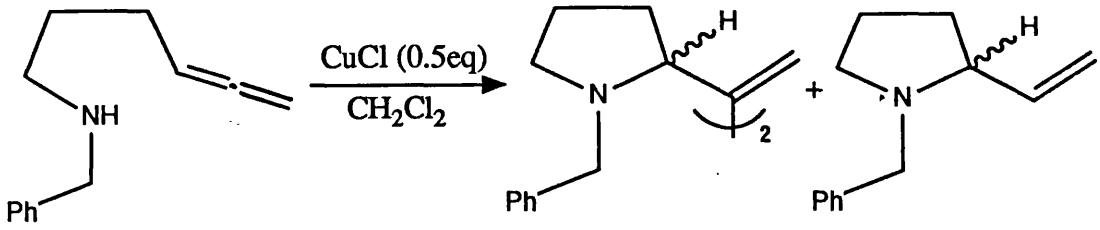
Dichloromethane proved to be a more appropriate solvent for these transformations and within 2h at room temperature, **(90)** was once again converted to the product mixture **(168)** in the presence of 2 equivalents of copper(I) chloride. Similarly, smooth reaction of **(88)** was observed at room temperature within 12h to form the product mixture **(169)**, (Scheme 123), the structure of which was confirmed, as before, by C.I. mass spectral analysis.

Related coupling reactions have been reported by Whitesides[143] following thermal decomposition of vinylcopper(I) species in which copper(0) is formed as a byproduct. No analogous copper precipitation was observed in the cyclisation/dimerisations of **(88)** or **(90)** and this might indicate an alternative pathway to that suggested by Whitesides. Other studies[144] have been carried out in related areas since 1974, although mechanistic proposals for reactions of vinylcopper(I) species remain rather vague.



S-(88) (169) (170)

Scheme 124



(125) **(171a,b)** **(126)**

1.8 : 1 : 1.8

34%

Scheme 125

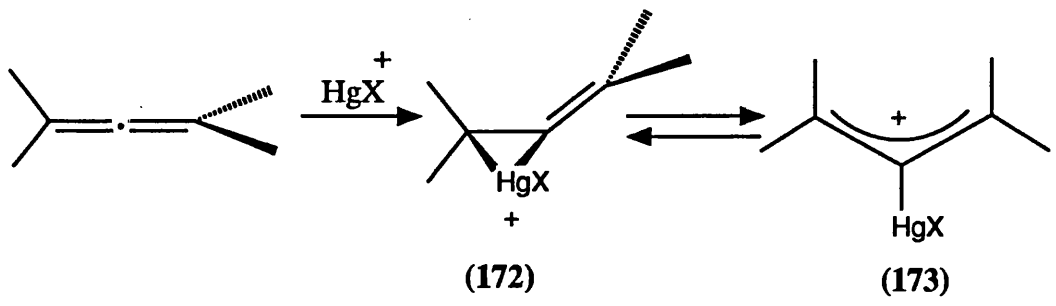
In an attempt to trap the intermediate organocuprate prior to coupling, **(88)** was combined with copper(I) chloride in ethyl acrylate as solvent (Scheme 124). It was intended that the intermediate vinylcopper species would undergo 1,4 addition to the α,β-unsaturated ester more rapidly than dimerisation. Formation of the ethyl ester **(170)** would then provide a rapid entry into a valuable intermediate required for the total synthesis described in later sections. In the event, only the products of dimerisation were observed with a similar diastereoisomer distribution to that obtained in dichloromethane.

To simplify analysis of the reaction products, the achiral cyclisation precursor **(125)** was employed as a substrate for copper(I)-mediated dimerisation (Scheme 125). In the presence of 0.5 equivalents of copper(I) chloride in dichloromethane, the two diastereomeric products of cyclisation/dimerisation **(171a,b)** were obtained as a 1.8:1 mixture, along with the vinylpyrrolidine **(126)** after 5h. The dimeric species were isolated, characterised separately and are included in the experimental section. The formation of the vinylpyrrolidine **(126)** would appear to suggest the mediation of a modified copper species, released as a byproduct of the cyclisation/dimerisation sequence. The participation of copper(II) chloride in this process was excluded by attempting cyclisation of **(90)** in dichloromethane, in the presence of stoichiometric copper(II) chloride. After 6h at room temperature, clean starting material was recovered quantitatively.

Although no further applications were explored in this area, the use of copper(I) species to mediate the cyclisation of the allenic amine substrates would appear to be a very promising transformation which, under appropriate conditions, could be expected to lead to highly functionalised products.

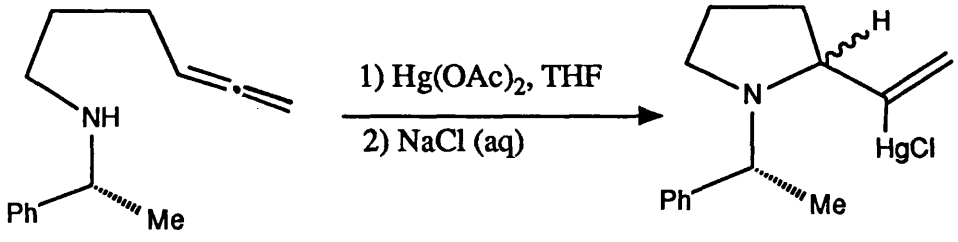
2.64(ii) Mercury(II)-Mediated Cyclisations

Mercury(II) salts have been a common choice for electrophile promoted additions to double bonds either in cyclisations[145] or in intermolecular transformations[146] and their popularity arises from the stability of the organomercurial products and their ability to undergo subsequent transformation.[147] Mechanistic investigations have been undertaken to determine whether the transformations involving allenes occur by way of a bridged intermediate **(172)** or an open allylic cation **(173)**[148, 73b] (Scheme 126) and how the choice of mercury(II) salt influences the pathway adopted.[149] It was found that formation of a planar, π-allyl cation intermediate is favoured by the presence of electronegative atoms (e.g. X = Cl) attached to mercury, that destabilise positive charge on the metal.



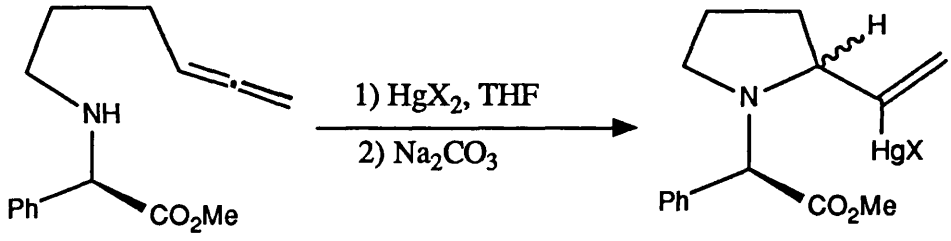
(172) **(173)**

Scheme 126



R-(88) (174a,b)

Scheme 127



(89) (175a,b)

X = OAc, 93% (1:1)

= CF_3CO_2, 85% (1.4:1)

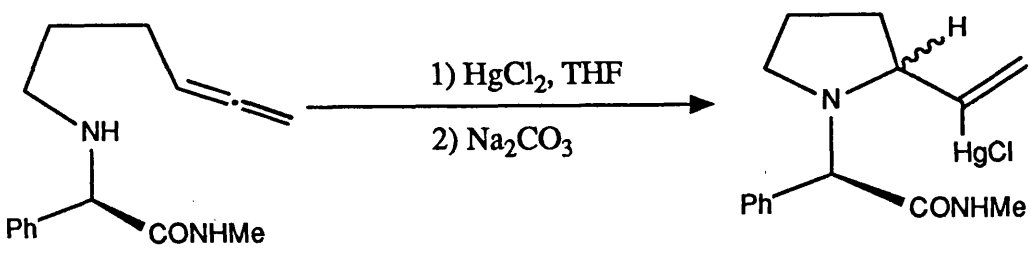
= Cl, 66% (4:3)

Scheme 128

Initial experiments to examine the mercury(II)-promoted aminocyclisations of the allenic amine substrates were carried out using the α-methylbenzyl derivative **(88)** (Scheme 127). Addition of 2 equivalents of mercury(II) acetate to a solution of the amine in THF effected complete conversion to the vinylmercuric acetate **(174a,b)**, as indicated by t.l.c.. Work-up included a brine wash which converted the salt to the corresponding chloride, as evidenced by peaks around 436 in the mass spectrum. Proton NMR of the crude reaction mixture established the diastereomeric ratio as 1.6:1.

The methyl ester **(89)** was also used as a cyclisation substrate. Exposure to mercury(II) acetate (1 equivalent) in THF, followed by the addition of sodium carbonate (1.2 equivalents) after 30 min. afforded the vinylmercuric acetate **(175a,b)** in high yield as a 1:1 mixture of diastereoisomers (Scheme 128, X=OAc). Work-up of the reaction mixture involved concentration *in vacuo* followed by dilution with dichloromethane, filtration and concentration of the filtrate *in vacuo*. In all the examples described, the vinylmercury(II) salts were colourless solids and could be used for subsequent functionalisation without further purification (*vide infra*).

Use of mercury(II) trifluoroacetate in a similar reaction sequence afforded the cyclised vinylmercuric trifluoroacetate in 85% yield as a 1.4:1 mixture of diastereoisomers (Scheme 128, X=CF_3CO_2). A similar ratio was achieved employing mercury(II) chloride as the electrophile; this led to a vinylmercuric chloride **(175a,b)** (X=Cl) which could be purified by silica gel chromatography. Thus, the use of the more strongly electron-withdrawing counterions (trifluoroacetate and chloride) had only a marginal influence on the stereochemical course of the cyclisation.



(90)

(176a,b) (1.3:1)

70%

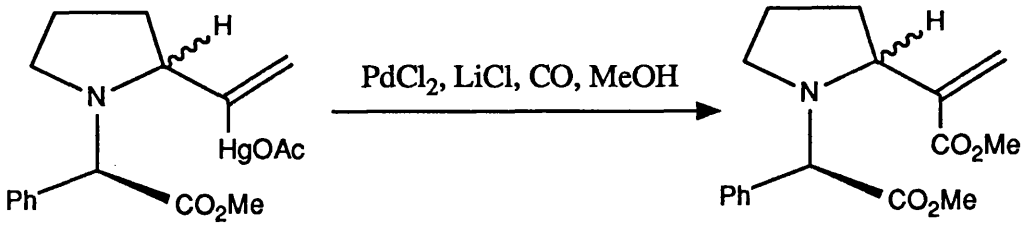
Scheme 129

Addition of mercury(II) chloride to the amide **(90)** led to the formation of the vinylmercuric chloride **(176a,b)** as a 1.3:1 mixture of separable diastereoisomers (Scheme 129). Chromatography effected isolation of the separated products in a combined yield of 70%, although rapid decomposition in deuterochloroform was evident. The mercury(II)-mediated cyclisation of the diamine **(100)** led to products which decomposed too rapidly to allow characterisation.

At this stage, experiments were carried out in an attempt to extract mechanistic information concerning the mercury(II)-mediated cyclisations and thus to improve on the rather disappointing diastereoselectivities that had been achieved. It was found for the process illustrated in Scheme 129 that the ratio of products obtained was unaffected by the order of addition of sodium carbonate and mercury(II) chloride. This contrasts with analogous iodine-mediated cyclisations of unsaturated alcohols in which kinetic and thermodynamic conditions are distinguished.[150] Furthermore, no diastereoisomer interconversion was observed on heating under the reaction conditions. These results would appear to suggest that product formation is under kinetic control.

To explore the possibility of the vinylmercuric chloride product acting as the electrophilic trigger for cyclisation, the amide substrate was combined with 0.5 equivalents of mercury(II) chloride. Prolonged reaction led to the formation of the usual product **(176a,b)** and recovered starting material; no bis-vinylmercuric species were detected over a 24h period.

Although the mercury(II)-mediated cyclisations proceeded with poor diastereoselectivities, the transformations were clean and led to relatively stable vinylmercuric intermediates in good yield. The next section describes



(175a,b) (1:1)

(145a,b) (1:1)

62%

Scheme 130

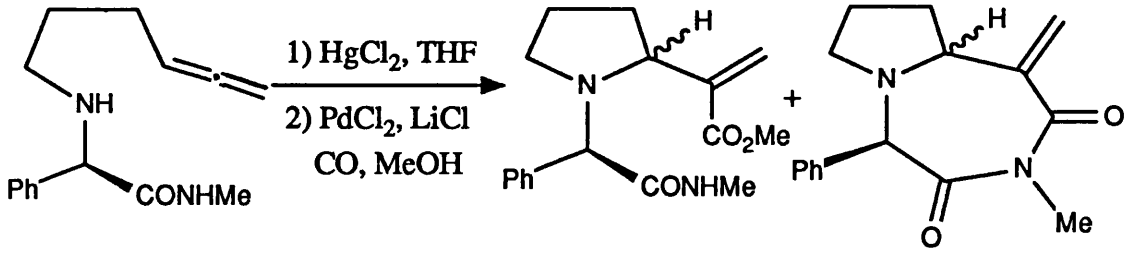
how the synthetic utility of these salts was exploited and in doing so, how stereochemical correlations with the silver(I)-mediated cyclisation and mechanistic information concerning the palladium(II)-mediated process were derived.

2.6 (iii) Functionalisation of the Cyclised Vinylmercuric salts

In establishing the versatility of the vinylmercuric products of cyclisation, demonstration of their conversion to the acrylate methyl ester products of the palladium(II)-mediated cyclisation became a central issue. Larock describes metal-metal exchange following the addition of stoichiometric palladium(II) chloride/lithium chloride to a solution of the vinylmercuric salt, resulting in the formation of the corresponding vinylpalladium species.[151] Under carbomethoxylation conditions, this leads to the acrylate ester as before. A similar strategy has, very recently, been adopted by Walkup[74a] in which catalytic palladium(II) chloride, in the presence of stoichiometric copper(II) chloride, is employed to effect transmetallation.

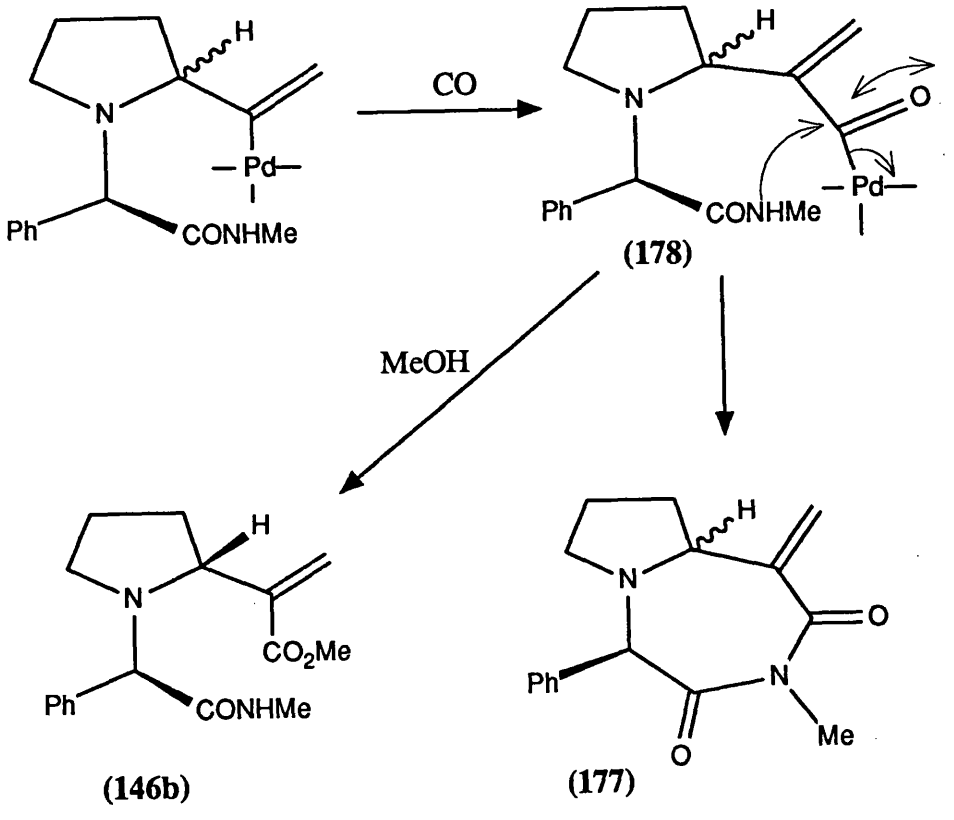
Application of Larock's conditions to the vinylmercuric chloride **(174a,b)** was unsuccessful in effecting conversion to the acrylate methyl ester **(144a,b)**. However, the vinylmercuric acetate **(175a,b)** (X=OAc) derived from the ester **(89)**, under similar reaction conditions led to the isolation of the desired products **(145a,b)** as a 1:1 diastereomeric mixture and a yield of 62% following chromatography (Scheme 130). The moderate yield obtained in this reaction and the difficulty in isolating products from the reaction of **(174a,b)** could be attributed to the use of activated carbon to remove the precipitated palladium(0). More efficient transformations might be expected using catalytic palladium(II) although this possibility was not explored.

Complications arose with the use of the cyclised amide (**176a,b**) in the metal-metal exchange under carbomethoxylation conditions. Rather than the expected 1.3:1 mixture of two diastereomeric acrylate products being observed, only one of these was actually detected in the reaction mixture. Also isolated from the reaction mixture was an inseparable diastereomeric mixture of products, the structure of which has been assigned as (**177**) (Scheme 131).



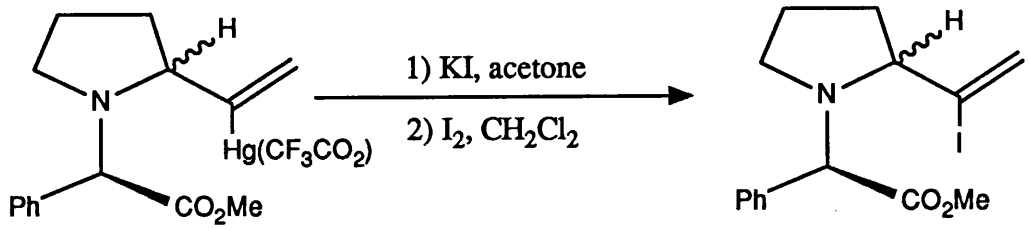
(**90**) (**146b**) 20% (**177**) (6.7:1) 9%

Scheme 131



Scheme 132

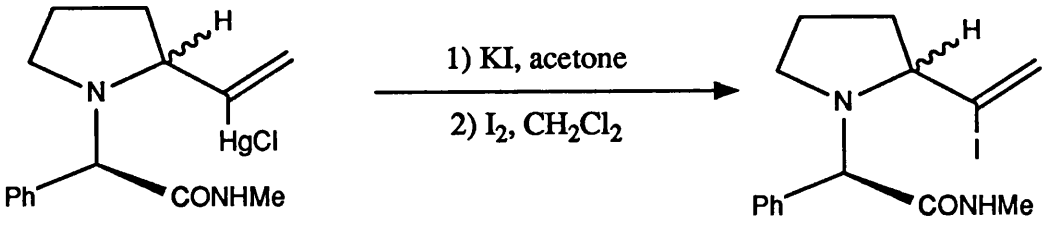
The bicyclic structure of **(177)** has been confirmed by proton NMR, IR and mass spectrometry and might reasonably result from nucleophilic attack by the amide nitrogen on the acyl palladium species **(178)** following carbonyl insertion (Scheme 132). Analogous formation of cyclic imides has been observed previously in palladium(II)-mediated carbonylations[152] and with systems involving acylcobalt[153] or acylnickel[154] intermediates. It would appear that for one diastereoisomer of **(178)** intramolecular trapping is very much more rapid than solvolysis whereas for the other diastereoisomer, these proceed at comparable rates. This would explain the formation of **(146b)** as a single diastereoisomer but **(177)** as a mixture. Dreiding models[155] indicate that the formation of the diastereoisomer **(177)** with (S)-configuration at the ring junction would be expected to be more favourable owing to the coplanarity of the four contiguous sp^2 centres comprising the enone and amide subunits. Such an arrangement cannot be adopted in the diastereoisomer with (R)-configuration at the ring junction. It is likely, therefore, that the corresponding cyclised acyl palladium leads to the product of carbomethoxylation with (R) configuration at C2 of the pyrrolidine ring. That this process is completely absent from the cyclisation/carbomethoxylation of **(90)**, mediated directly by palladium(II), is an indication that in this latter process, carbonyl insertion and ensuing methanolysis occurs more rapidly than cyclisation. If this were not the case, formation of the cyclised acyl palladium intermediate **(178)** and subsequent isolation of **(177)** would be expected. This piece of mechanistic evidence is a necessary factor in explaining the poor diastereoselectivities observed with the palladium(II)-mediated process (Section 2.5 (iii)). The relative rates of methanolysis and intramolecular nucleophilic attack appeared to be dependent on reaction conditions since, in a second experiment, employing 0.99 equivalents of palladium(II) chloride (compared with 1.1 equivalents for the first experiment), a 4:1 mixture of **(177)** was obtained in 10% yield.



(175a,b)

(179a,b)
62%

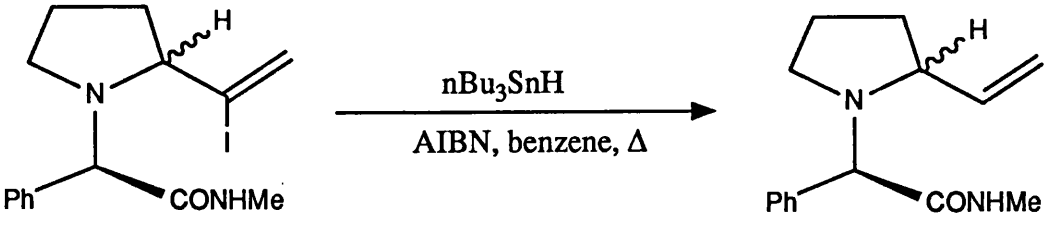
Scheme 133



(176a,b)

(180a,b)
53%

Scheme 134



(180a,b) (11:1)

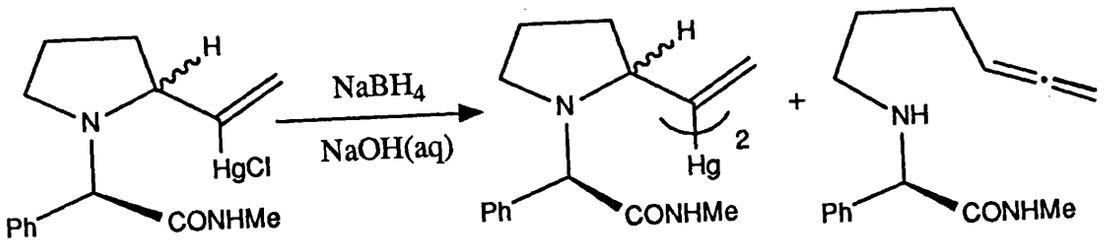
(105a)
27%

Scheme 135

Conversion of vinylmercuric salts to synthetically versatile vinyliodide compounds was achieved, as indicated in Scheme 133, employing the procedure of Harding.[147b]

Transformation of **(175a,b)**, derived from the ester **(89)** resulted in the formation of the vinyl iodide **(179a,b)** as a mixture of diastereoisomers reflecting the selectivity in the initial mercury(II)-mediated cyclisation. Similar treatment of **(176a,b)** (4:1 mixture of diastereoisomers) resulted in the formation of **(180a,b)** (Scheme 134). Chromatography allowed isolation of the vinyl iodide as an 11:1 mixture in 53% yield. To correlate the major product of the mercury(II) cyclisation **(176a)** with that of the silver(I)-mediated process, the vinyliodide was subjected to radical reduction (Scheme 135).

Thus, treatment of the product mixture **(180a,b)** with tri-*n*-butyltin hydride in refluxing benzene, in the presence of catalytic AIBN, effected conversion to the vinylpyrrolidine . The major isomer in the proton NMR spectrum of the reaction mixture correlated with **(105a)**, the major product of silver(I)-mediated cyclisation and was isolated in 27% yield following chromatography.



(176a,b) **(181)** **(90)**

Scheme 136

Direct reduction of the cyclised vinylmercuric intermediates was attempted, but after investigating a variety of conditions, no reduced vinylpyrrolidine products were detected.

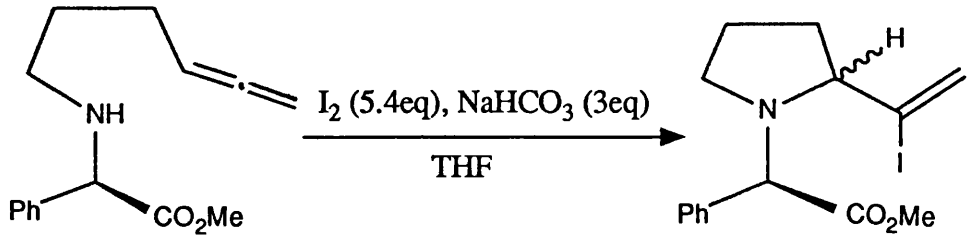
Addition of sodium borohydride in aqueous sodium hydroxide[156] to **(176a,b)** resulted in the formation of the bis-vinylmercury(II) species **(181)** as a mixture of diastereoisomers together with the cyclisation precursor **(90)** (Scheme 136). The assignment of **(181)** was confirmed by the presence of a molecular ion peak in the C.I. mass spectrum. Similar complications have been reported previously[97b] and in an attempt to circumvent these problems, the use of phase transfer conditions employing benzyltriethylammonium chloride as the catalyst have been introduced.[157] Whilst use of this procedure for the reductive demercuration of **(176a,b)** suppressed the ring cleavage side reaction, only products resulting from bis-vinylmercury(II) formation were observed.

The studies carried out employing mercury(II) as the electrophilic trigger have managed to demonstrate, in most cases, the synthetic potential of such transformations. However, the problems associated with the process, most notably the low diastereomeric excess obtained for the products, led to the investigation of non-metal electrophiles to induce cyclisation with the subsequent formation of stable and functionalised products. The next section discusses the work undertaken in this area.

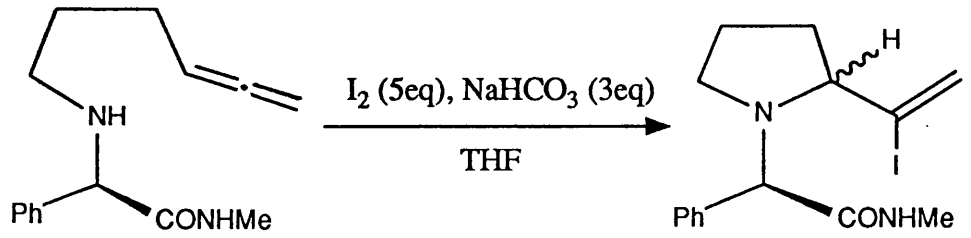
2.7 Use of Non-Metal Electrophiles

2.7 (i) Iodine and Bromine

Iodine-mediated cyclisations under either kinetic or thermodynamic conditions have been widely used in the stereoselective generation of oxygen-containing heterocycles.[158] Application of kinetic cyclisation conditions to the substrates **(89)** and **(90)** effected clean conversion to the desired cyclised iodides with moderate diastereoselectivity (Scheme 137). The cyclisation of the amide **(90)** afforded **(180a,b)** as a 3:1 mixture of inseparable diastereoisomers in 33% yield following chromatography. The major vinyliodide was correlated with the minor product of mercury(II)-mediated cyclisation followed by vinyliodide formation (Scheme 134). This leads to the conclusion that the sense of induction in the iodine-mediated cyclisation of the amide **(90)** is opposite to that for either the mercury(II)- or silver(I)-mediated transformations.

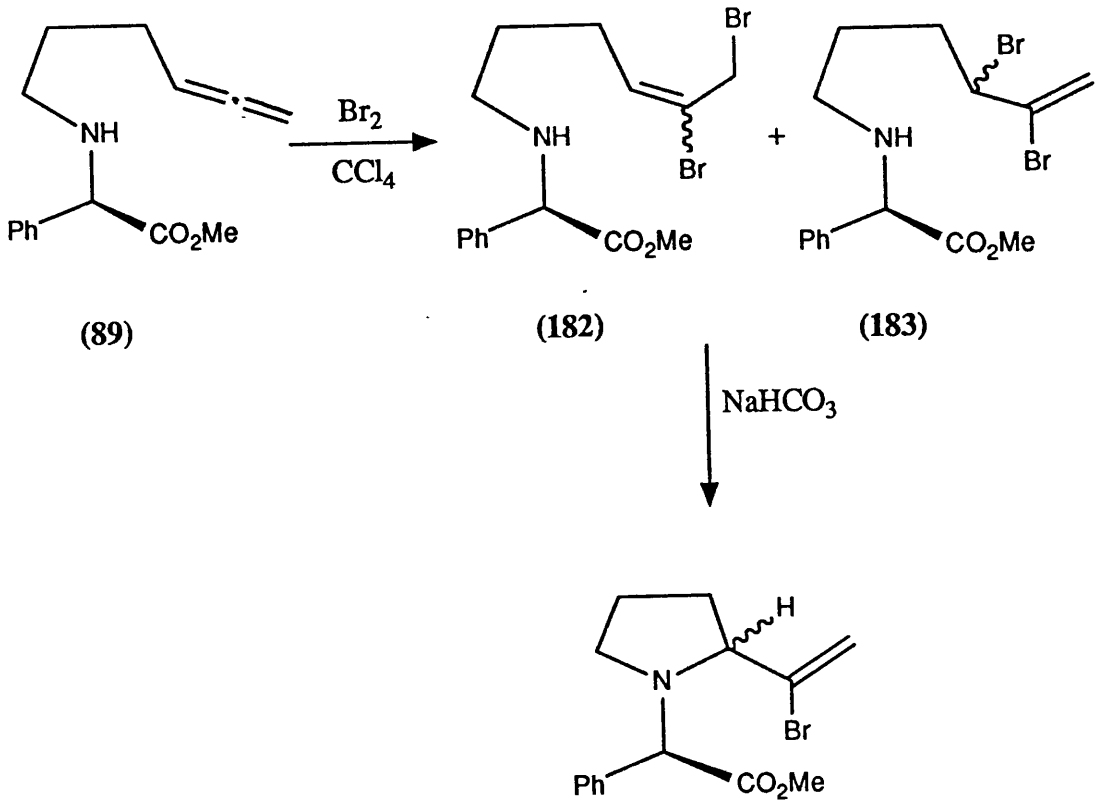


(89) **(179a,b)** (2:1)
62%



(90) **(180a,b)** (1:3)
33%

Scheme 137



(89) **(182)** **(183)**

(184a,b) (2:1)
77%

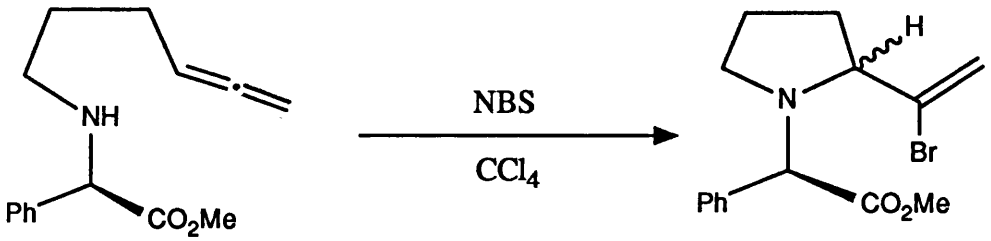
Scheme 138

The stereochemical course of cyclisations of γ,δ-unsaturated alcohols, mediated by bromine, has been studied by Monkovic.[159] The cyclisation is deemed to proceed through a bromonium ion with the stereochemical preference in the product reflecting the minimisation of steric repulsions between the bromonium ion and ring substituents in the transition state.

The bromine mediated cyclisation of the ester **(89)**, as evidenced by t.l.c., appeared to proceed *via* the bromine adducts **(182)** and **(183)** (Scheme 138). Addition of excess sodium bicarbonate was required for complete conversion to the cyclised vinylbromide **(184a,b)** which was obtained as a 2:1 mixture of diastereoisomers. The stereochemical integrity of the phenylglycine portion of the substrate **(89)** was unaffected by the presence of excess sodium bicarbonate as evidenced by comparison of optical rotation values prior and subsequent to stirring with sodium bicarbonate in dichloromethane for 4h at room temperature. The moderate levels of diastereoselectivity obtained with the use of halogens as electrophiles lend support to a mechanistic rationale similar to the *syn*-chloropalladation process described in section 2.5(iii). Initial addition of the halogen to the allene double bond would, once again, not be expected to be under diastereoface control by the existing stereogenic centre and subsequent cyclisation results in products with low stereoselectivity.

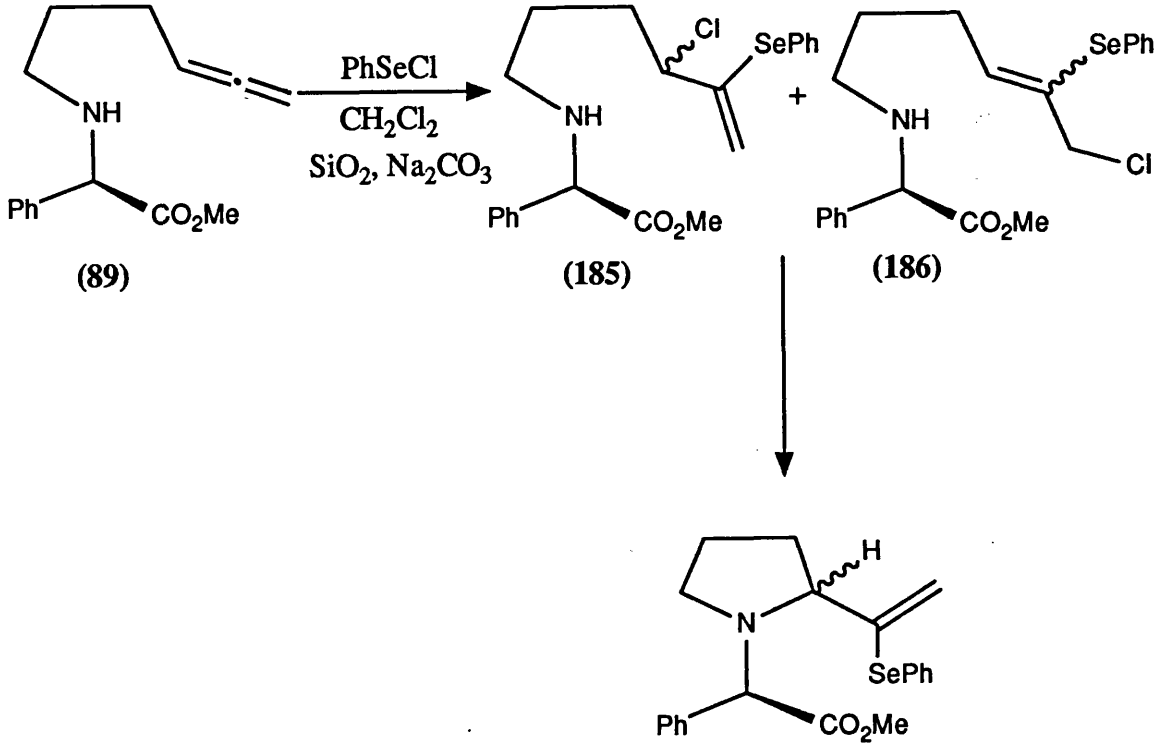
2.7(ii) *N*-Bromosuccinimide (NBS)

Successful use of an electrophilic bromine species such as NBS to effect cyclisations has been the subject of various studies[160] and adaptation of such methods to the cyclisation of the allenic amine **(89)** proved equally fruitful (Scheme 139). Clean and efficient conversion to the cyclised vinylbromide **(184a,b)** was observed although the product mixture reflected a lack of diastereoselectivity in the transformation. Once again, the poor stereochemical induction may be attributed to non-face selective attachment of the Br^+ species to the allene π-system. This in turn would result from an absence of pre-coordination by the aminoester portion to the electrophile.



(89) **(184a,b)** (1:1)
77%

Scheme 139


PhSeCl
CH_2Cl_2
SiO_2, Na_2CO_3
NH
Ph
CO_2Me
Cl
SePh
+
H
N
(89)
(185)
(186)
(187a,b) (3:2)
92%

Scheme 140

2.7(iii) Phenylselenenyl Chloride

Cyclisation involving phenylselenoetherification across double bonds of unsaturated alcohols, a method developed by Nicolaou, is an efficient and versatile procedure for the synthesis of oxygen-containing heterocycles.[109] The analogous process, introduced by Clive, involving aminocyclisation, has proved to be equally valuable.[161] Initial addition across the double bond by the selenium reagent is proposed, followed by ring closure, facilitated by silica gel. Sharpless has discriminated between kinetic and thermodynamic cyclisation conditions mediated by phenylselenenylbromide, which depend on the presence or absence of stoichiometric quantities of base.[162]

In the presence of excess sodium carbonate and silica gel, a solution of the methyl ester **(89)** in dichloromethane underwent cyclisation mediated by stoichiometric phenylselenenyl chloride. The reaction proceeded through an intermediate species, as indicated by t.l.c., and this is presumed to be either or both the addition products **(185)** and **(186)** (Scheme140). After 2 days at room temperature, complete conversion to the separable cyclised vinylselenides **(187a,b)** as a 3:2 ratio was effected in 92% yield following chromatography.

Once again, inadequate face discrimination during the initial addition step could be responsible for the poor level of diastereoselectivity observed in the product.[163]

This section has demonstrated how a range of non-metal electrophiles may be employed to induce cyclisation of the γ-allenic amine substrates. In all cases, the products formed are conducive to further elaboration although the degree of stereochemical induction shows no significant improvement on the palladium(II)- or mercury(II)-mediated processes.

The remainder of this discussion focusses on the exploitation of the methodology developed in the preceding sections for the formation of enantiomerically pure synthetic intermediates of the type **(84)**. In particular, elaboration of **(144b)**, the diastereomerically pure product of palladium(II)-mediated cyclisation/carbomethoxylation, to the indolizidine skeleton will be described, highlighting its key role in the enantioselective approach to pumiliotoxin 251D.

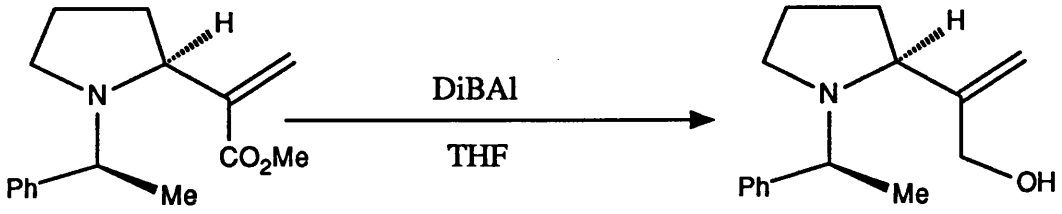
2.8 Construction of the Indolizidine Skeleton

2.8(i) Bicyclic Lactam Formation

Two important features associated with the palladium(II)-mediated cyclisation of the allenic amine substrates were the high yield of products obtained and their ability to undergo further chemical transformation. The diastereomeric products of cyclisation of **(88)** could be readily separated on a large scale, affording multigram quantities of either **(144a)** or **(144b)** in isomerically pure form. Thus, the α-methylbenzyl residue, despite its inability to induce asymmetry at the newly-formed ring junction, fulfils the role of an internal resolving agent in a highly efficient manner.

Although at this stage, the absolute stereochemistry at the C2 ring position in each diastereoisomer remained unknown, it was decided to proceed with **(144b)** for elaboration to the azabicyclic framework required for the natural product **(7)**. Stereochemical information derived from an X-ray structure obtained on a more advanced intermediate established that the choice of **(144b)** had indeed served to establish the required (S)-stereochemistry at C8a of pumiliotoxin 251D (*vide infra*).

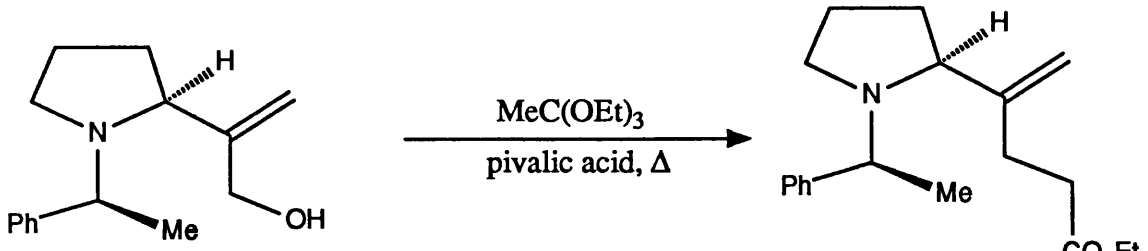
The acrylate subunit in **(144b)** provided an expedient route to the bicyclic lactam **(77)** through the series of transformations described below.



(144b) **(188)**

98%

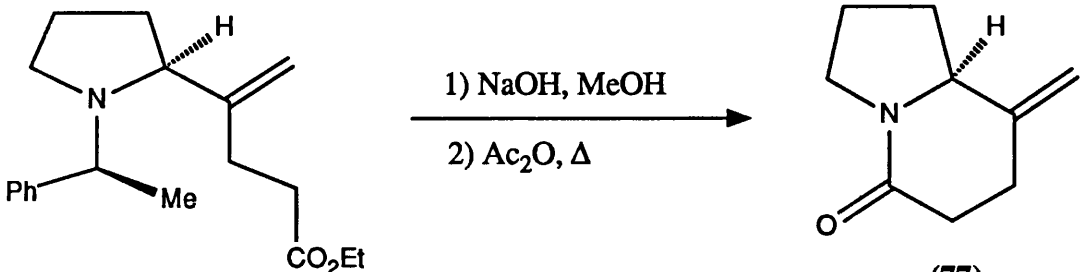
Scheme 141



(188) **(170)**

95%

Scheme 142



(170) **(77)**

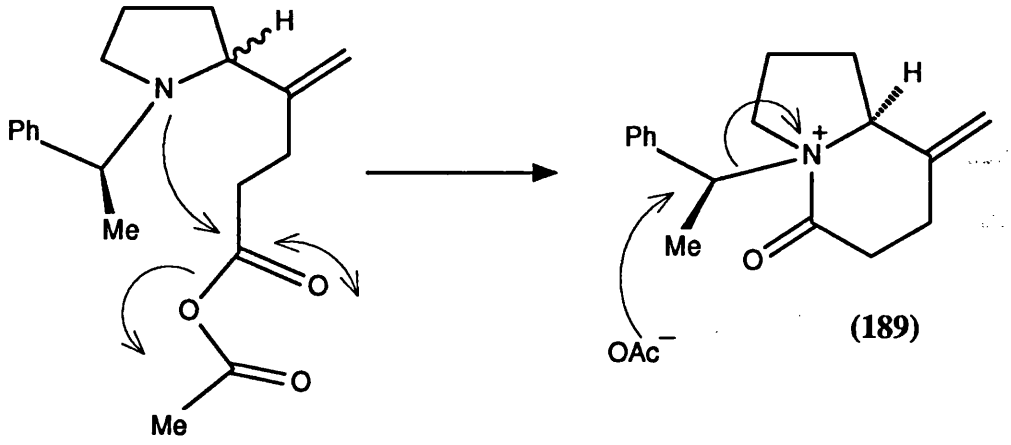
76%

Scheme 143

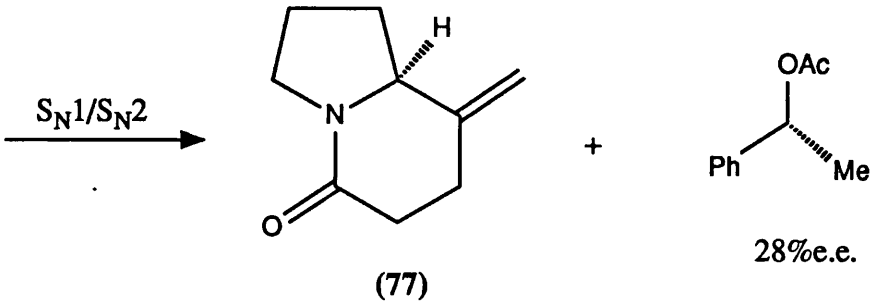
Addition of DiBAL to the α,β-unsaturated ester effected clean conversion to the corresponding allylic alcohol **(188)** which could be used in the next step without special purification (Scheme 141). Homologation of **(188)** to the required ethyl ester **(170)**, involved participation of the olefinic double bond; a valuable legacy of the allene-based cyclisation. Treatment of **(188)** under Claisen orthoester rearrangement conditions[164] allowed isolation of **(170)** in 95% yield in diastereomerically pure form, as indicated by proton NMR (Scheme 142).

This product contains all the necessary components for lactam formation following appropriate activation of the carbonyl functionality. Such activation was achieved by employing the two-step procedure illustrated in Scheme 143.

Basic ester hydrolysis followed by mixed anhydride formation in refluxing acetic anhydride led directly to the bicyclic lactam **(77)** in 76% yield. The removal of the last traces of methanol remaining from the hydrolysis step was essential if formation of the methyl ester analogue of **(170)** by a competing reaction pathway was to be avoided. The transformation described accomplishes two major objectives; it allows construction of the bicyclic framework as well as effecting cleavage of the stereogenic control element.



(189)



(77)

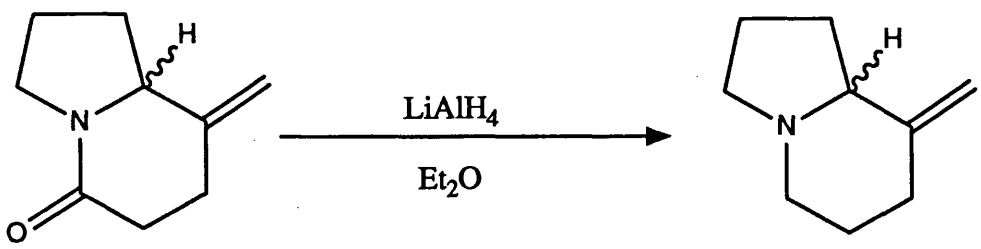
28%e.e.

Scheme 144

It was initially believed that this cleavage proceeded *via* an elimination mechanism (E_1or E_2) involving the formation of styrene as a byproduct. The absence of styrene in the reaction medium along with the isolation of α-methylbenzyl acetate as a co-product pointed to an alternative reaction mechanism which is outlined in Scheme 144. The proposed intermediate acylammonium species **(189)** leads to the desired lactam **(77)** following nucleophilic displacement at the benzylic carbon by acetate ions present in the reaction medium. Such cleavage mechanisms have been observed in other systems involving lactam formation[127] and are closely related to the von Braun reaction pathway.[165] It is postulated that these processes may arise by way of S_N1 or S_N2 displacement, depending on the nature of the substrate. The latter would require that α-methylbenzyl acetate be isolated in optically pure form with overall inversion of stereochemistry. Conversely initial carbocation formation would lead to a racemic product. The optical purity of the α-methylbenzyl acetate was determined by two independent techniques and led to a value for the optical purity of 28% e.e..

Proton NMR analysis in the presence of 0.3 equivalents of the chiral shift reagent $Eu(hfc)_3$ resulted in complete resolution of two doublets at 2.76 and 2.83 p.p.m. corresponding to the benzylic methyl signals for the two enantiomers. Comparison of the integrals for each of these signals indicated a 1.7:1 ratio of optical isomers.

The optical rotation of the product was also obtained leading to $[\alpha]^{25}_D$ values of +35.9° (c 2.5, benzene) and +34.4° (c 3.3, benzene). Comparison with literature values[166] for (R)-α-methylbenzyl acetate confirmed the e.e. value determined by proton NMR and indicated net inversion at the benzylic centre.



(77) **(190)**

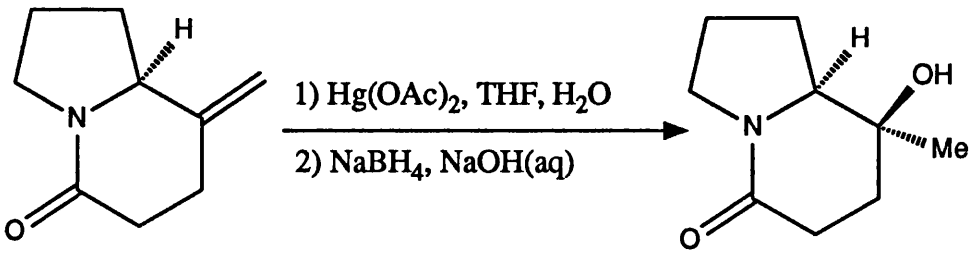
Scheme 145

It had been ascertained by NMR analysis that the ethyl ester leading to lactam **(77)** was diastereomerically pure. It remained to establish that the bicyclic lactam, having lost an asymmetric centre, was now enantiomerically pure and that the steps leading to its formation had not induced epimerisation at the C2 ring position. An unsuccessful attempt to demonstrate this maintenance of optical integrity involved application of Villani's procedure for the determination of the optical purity of tertiary amines.[112] Reduction of optically impure lactam **(77)** (derived from the mixture of acrylate methyl ester products **(144a,b)**) with lithium aluminium hydride in ether brought about conversion to the corresponding amine **(190)** (Scheme 145). Combination of this product with 1.1 equivalents of R-(+)-MTPA and analysis by proton NMR indicated no observable splitting of signals and so proved to be an ineffective method for the determination of optical purity in this system. Successful evaluation of e.e. was, however, achieved following functionalisation of the olefinic double bond (*vide infra*).

2.8(ii) Hydration of the Exocyclic Double Bond

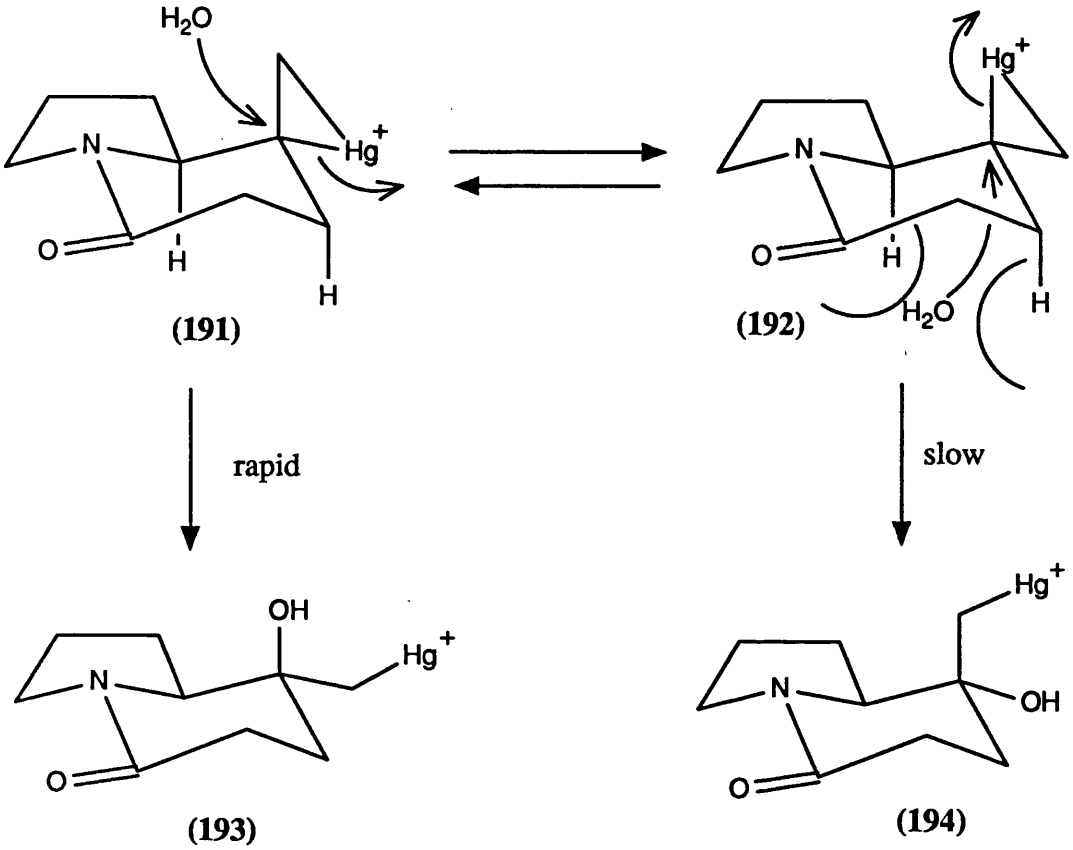
The bicyclic lactam **(77)** is a crucial synthetic intermediate; it allows introduction of the tertiary hydroxyl functionality present in the target, as well as housing a carbonyl moiety which acts as a vehicle for the incorporation of the alkylidene side chain at C6 *via* an aldol/elimination sequence.

This section describes the use of a selective hydration procedure, developed by Brown,[167] that fulfils the first of these roles in a highly efficient manner. Scheme 146 shows how application of a hydroxymercuration/reduction sequence to lactam **(77)** executes efficient conversion to hydroxylactam **(75a,b)** as a 10:1 mixture of diastereoisomers. The minor component could be cleanly removed by a single recrystallisation to afford the diastereomerically pure tertiary alcohol in 60% yield. The reaction is believed to proceed *via* an intermediate bridged mercuronium ion with water attacking the more highly substituted carbon atom, resulting in formation of the tertiary alcohol. No regioisomeric products were observed in the reaction mixture.



(77) **(75a,b)** (10:1)
95%

Scheme 146


H2O
Hg+
N
O
H
H
(191)
Hg+
N
O
H
H2O
H
(192)
rapid
slow
OH
Hg+
N
O
(193)
Hg+
OH
N
O
(194)

Scheme 147

The high stereochemical preference may be rationalised in terms of the model illustrated in Scheme 147. The two mercuronium ion intermediates **(191)** and **(192)** may be considered to be in rapid equilibrium and the orientation of attack by water is determined by their relative reactivities. Attack by water on the cationic species **(192)** requires approach that is hindered by two axial carbon-hydrogen bonds on either side of the reacting centre. Formation of the equatorial alcohol **(194)** is, therefore, sterically disfavoured. The diastereomeric mercuronium ion **(191)** is, however, susceptible to attack by water in a relatively unhindered manner to afford, more readily, the axial alcohol **(193)**. Thus, this model predicts the preferential formation of the tertiary alcohol with (S)-absolute stereochemistry which is that found in the natural product **(7)**.

The selective formation of the axial alcohol and the mechanistic rationale proposed are in accord with other studies carried out on related exocyclic and bicyclic alkenes.[168] Confirmation of the relative stereochemistry of the major alcohol isomer was obtained by the observation of n.O.e. enhancements in the proton NMR spectrum. Unambiguous stereochemical assignment was provided by the X-ray structure determination of a more advanced intermediate derived from the major hydroxylactam.

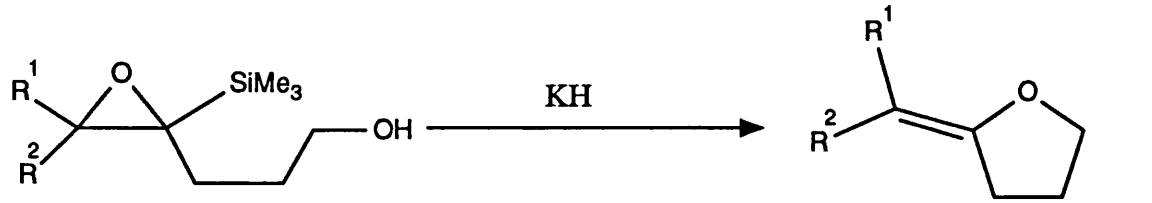
Hydroxylactam **(75a)** was considered more amenable to enantiomeric excess evaluation than the less functionalised unsaturated lactam **(77)** and for this reason, efforts were made to seek an appropriate technique for this function.

Mosher's acid (MTPA) and its corresponding acid chloride (MTPACl), in enantiomerically pure form, are reagents commonly used to derivatise alcohols and amines for the purpose of optical purity determination.[169] The

tertiary hydroxyl functionality in **(75a)**, however, appeared to be sufficiently sterically hindered to preclude acylation by the conventional procedure.

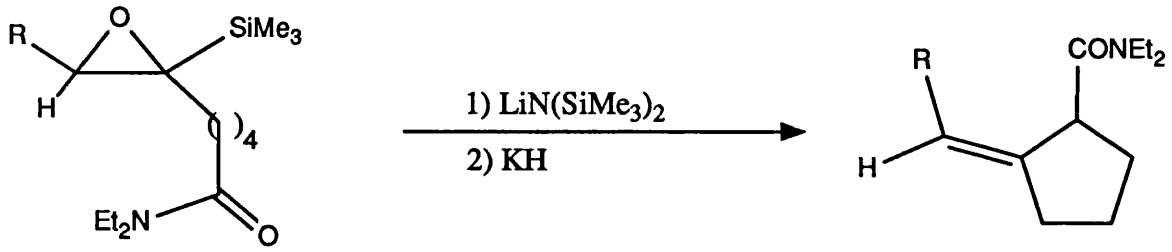
Successful determination of the optical purity of **(75a)** was achieved by proton NMR analysis of the diastereomerically pure axial alcohol in the presence of the chiral shift reagent $Eu(hfc)_3$. The optically impure hydroxylactam, derived from the diastereomeric mixture **(144a,b)**, was combined with 0.8 equivalents of the chiral shift reagent. This led to complete resolution of the signals for H8a and C8-Me corresponding to the two enantiomers present. Within the limits of detection, only one set of peaks were observed in the spectrum of the hydroxylactam derived from the single diastereoisomer **(144b)** under similar conditions. This experiment, therefore, confirms the preservation of optical integrity in all the intermediates leading to the key bicyclic hydroxylactam **(75a)**.

The following three sections illustrate how the second vital role of the unsaturated lactam **(77)** is realised; i.e. introduction of the Z-alkylidene side chain and how this leads to a successful completion of the total synthesis of pumiliotoxin 251D in optically pure form.

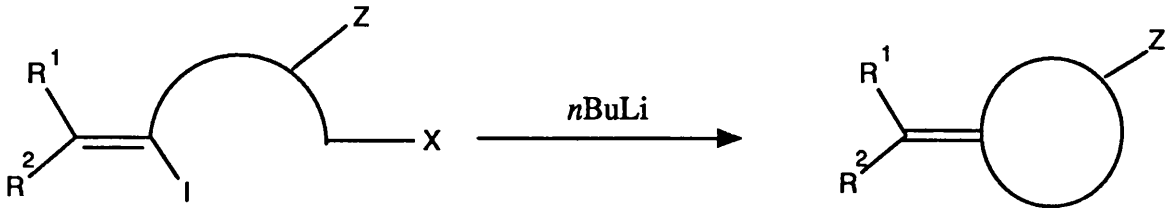


>95% retention of stereochemistry

Scheme 148



Scheme 149

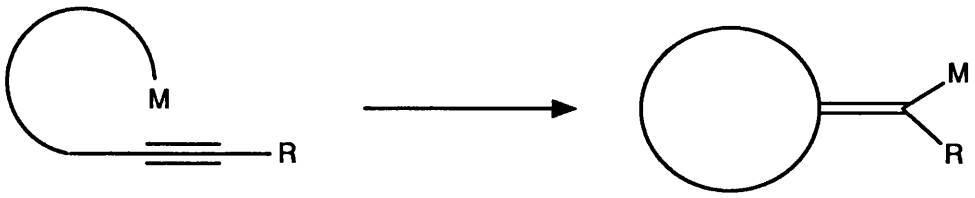


Scheme 150

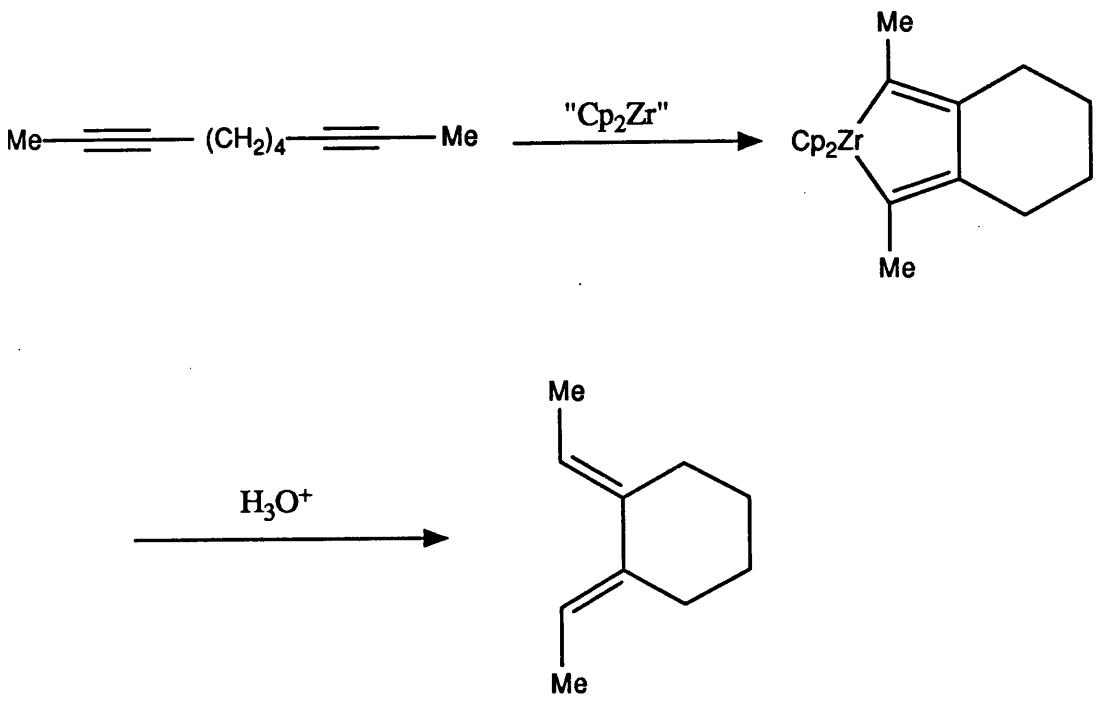
2.9 Model Studies on the Introduction of the Z-Alkylidene Side Chain

2.9(i) Introduction

The following two sections describe the development of methodology for the stereocontrolled creation of the Z-alkylidene subunit present in the natural product (**7**). Section 1.2 illustrated how this structural challenge was overcome in previous syntheses of pumiliotoxin A alkaloids and the problems associated with controlling exocyclic alkene geometry have also been recognised in a more general sense leading to a variety of solutions. Negishi[170], in particular, has devised a number of elegant approaches illustrated in Schemes 148-151.



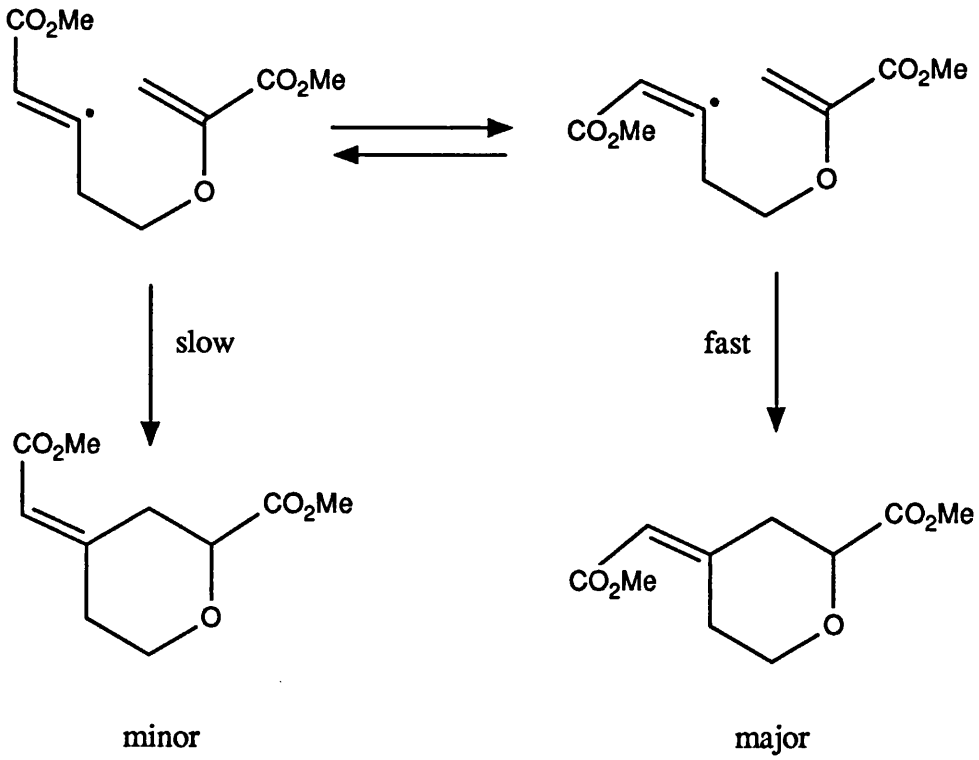
Scheme 151



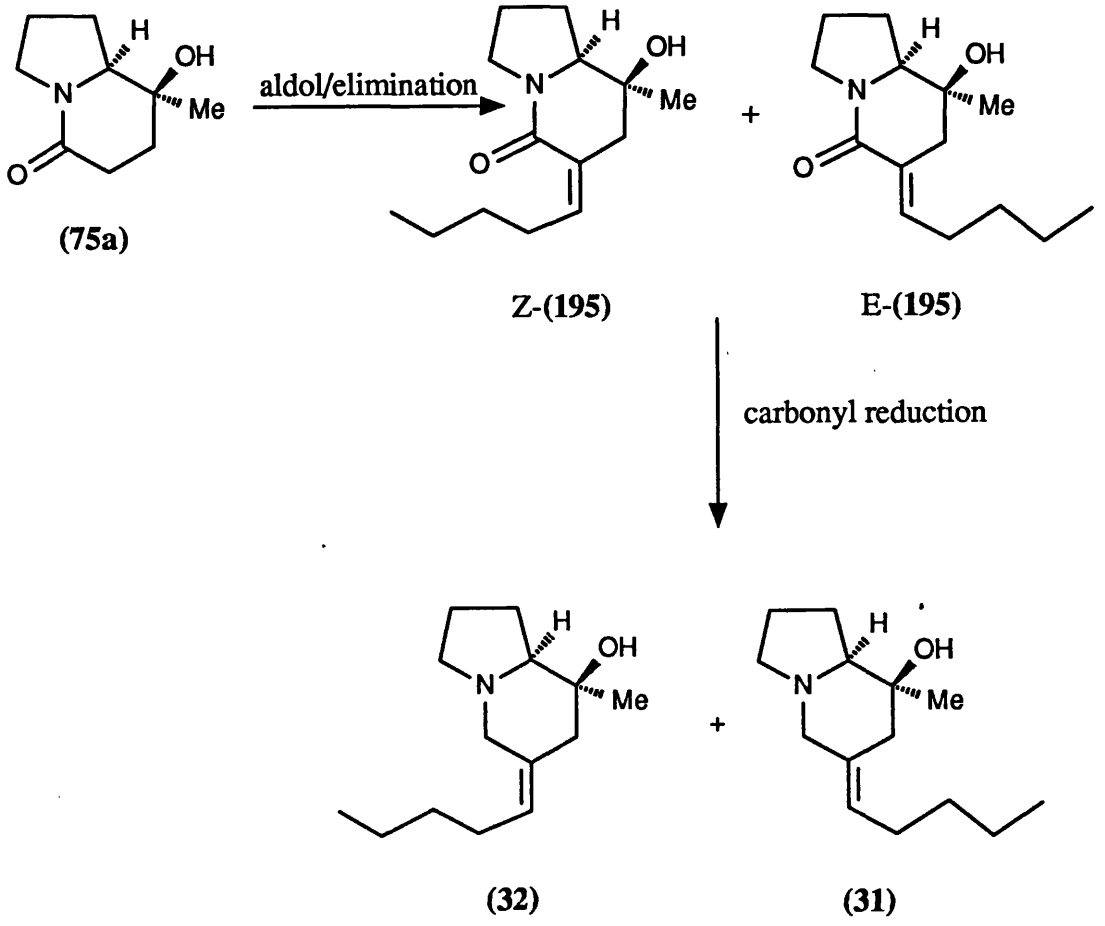
Scheme 152

Nugent has also been active in this field with the zirconium-mediated cyclisation of diacetylenes to form stereodefined dienes (Scheme 152).[171]

A range of approaches employing the Wittig procedure or modifications thereof have led to the successful control of double bond stereochemistry[172] and a radical cyclisation reported by Thomas[173] exhibited significant stereochemical bias attributed to rapid cyclisation of the relatively unhindered Z-vinyl radical (Scheme 153).



Scheme 153



(75a)

Z-(195)

E-(195)

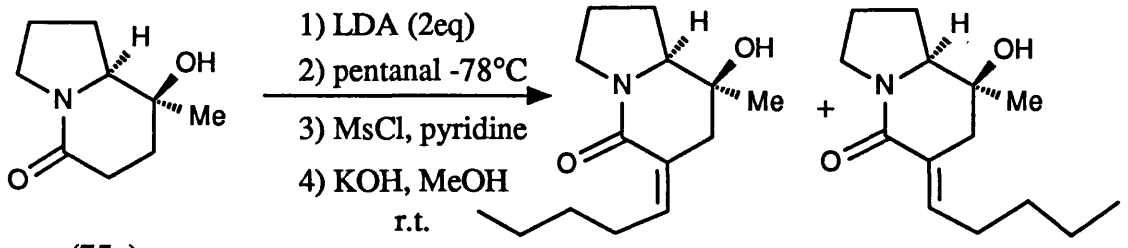
(32)

(31)

Scheme 154

The synthetic strategy adopted in this current synthesis, outlined in the retrosynthetic analysis (Scheme 57), seeks to employ an aldol/elimination sequence in which appropriate stereospecific elimination conditions lead to the preferential formation of Z-enelactam Z-(**74**). A similar sequence appeared in Overman's synthesis of the allopumiliotoxin A alkaloids[4c] (Scheme 8) but in this case, E-enone formation was a consequence of thermodynamic control. Since Z-(**74**) would be expected to be disfavoured thermodynamically with respect to the E-isomer,[174] the ultimate double bond geometry has to be established at a stage preceding the elimination step.

Control of alkene geometry prior to stereospecific *syn*-[175] or *anti*-elimination[176] has been used as a successful ploy in previous syntheses. In order to evaluate the viability of this strategy within the context of the proposed total synthesis, model studies were carried out initially, employing the achiral aldehyde pentanal. This enabled use of optically impure (**75a**), derived from the isomeric mixture (**144a,b**), whilst avoiding the complication of additional diastereomeric products. Moreover, the pumiliotoxin analogues (**31**) and (**32**) resulting from carbonyl reduction of the enelactams E- and Z-(**195**) have been synthesised and characterised by Overman[7b], thus providing a means of comparison (Scheme 154).



(75a)

Z-(195) **E-(195)**

1 : 2.3

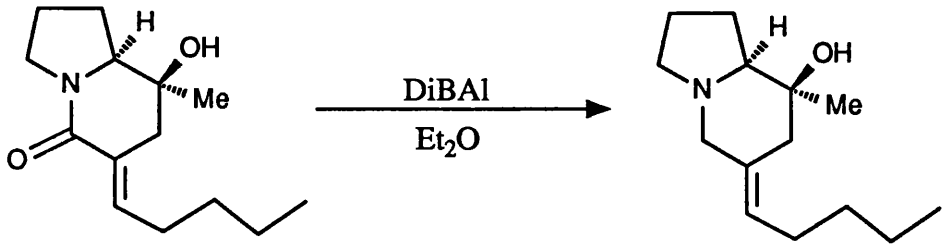
29%

Scheme 155

2.9(ii) Aldol/*Anti*-Elimination

Scheme 155 illustrates the aldol/elimination sequence adopted in which the initial aldol adduct mixture was subjected to selective mesylation of the secondary hydroxyl functionality followed by base-induced elimination.[176,177] The readily separable enelactams **(195)** were isolated in a combined overall yield of 29% with an E:Z ratio of 2.3:1.

Stereochemical assignment of the E- and Z-double bond geometry was made on the basis of proton NMR data. The vinyl proton signal for E-**(195)** was approximately 1 p.p.m. downfield of the corresponding signal for Z-**(195)**. This could be attributed to the anisotropic deshielding effect of the neighbouring carbonyl group in Z-**(195)**. Furthermore, the protons attached to C11 of Z-**(195)** were significantly further downfield than those of the E-isomer and exhibited more pronounced fine coupling to the equatorial proton (β-H) attached to C7 (*J* 2.5Hz) compared with E-**(195)** (*J* 1.5Hz). This evidence supports the assignments indicated in Scheme 155 and similar chemical shift patterns were seen in the enelactams E-**(74)** and Z-**(74)** (Section 2.10) which incorporate the chiral alkylidene side chain. In both systems, the enelactam assigned Z-geometry was considerably less polar than the E-isomer by silica gel chromatography. The E-double bond geometry of E-**(74)** was unambiguously established by X-ray analysis, lending further support to the assignments proposed for the model system.

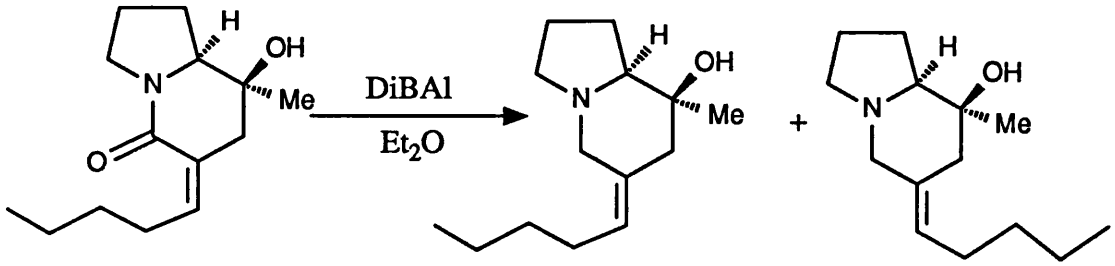


E-(195)

(31)

79%

Scheme 156



Z-(195)

(32)

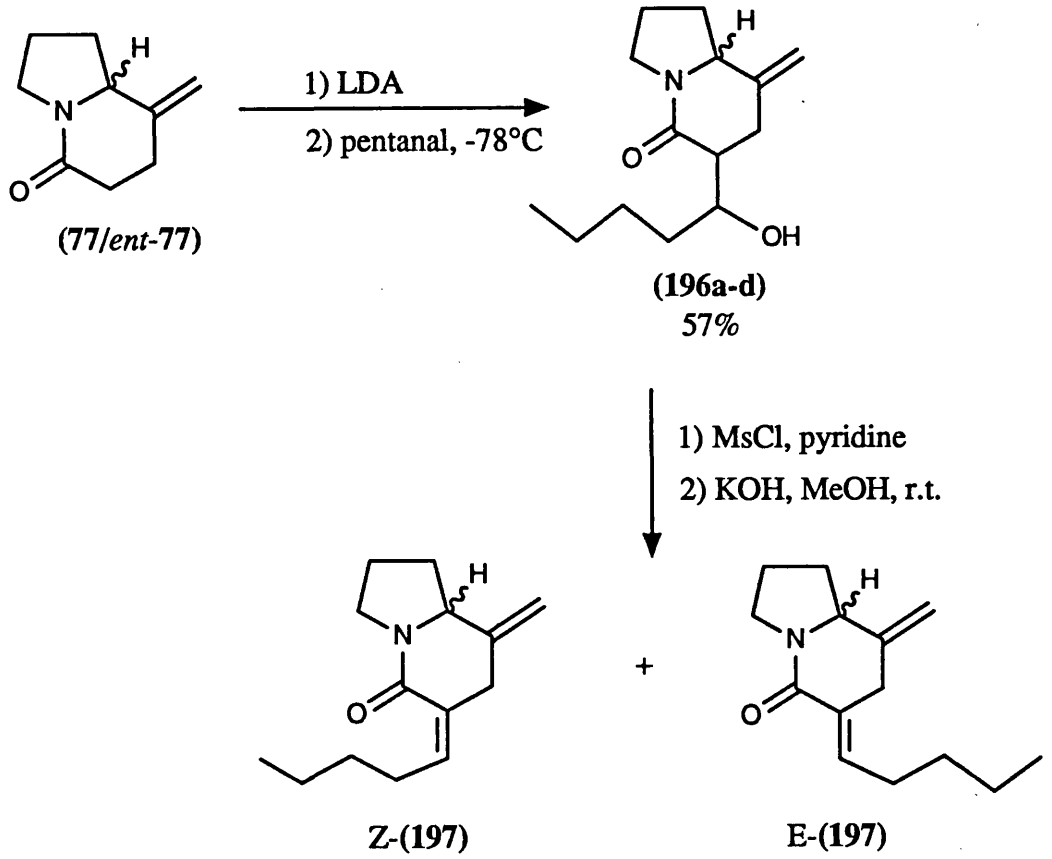
(31)

combined yield 83%

Scheme 157

The separated enelactams were each subjected to carbonyl reduction in order to correlate the products obtained with those synthesised by Overman (Schemes 156 and 157).[7b] Treatment of the E-enelactam with DiBAl[178] in ether effected clean conversion to the tertiary amine **(31)**. Reduction of the Z-enelactam resulted in the formation of a mixture of products; the major component was the desired Z-alkylidene tertiary amine **(32)**. The spectral data of both **(31)** and **(32)** were consistent with those previously reported by Overman.

However, also formed in the reduction of Z-**(195)** was **(31)**, a consequence of enelactam double bond isomerisation to the thermodynamically favoured E-geometry. The problems associated with carbonyl reduction of the Z-enelactam system in the context of the total synthesis are discussed in greater detail in section 2.11.



(77/*ent*-77)

(196a-d)
57%

Z-(197)

E-(197)

1 : 2.3

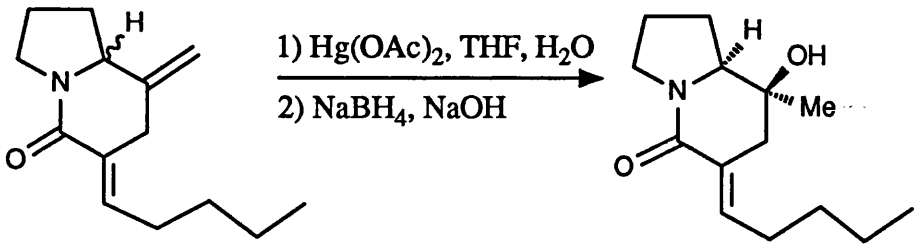
80%

Scheme 158

The remainder of this present section focusses on experiments carried out in an attempt to improve the Z:E-enelactam selectivity of the aldol/elimination sequence in the model system.

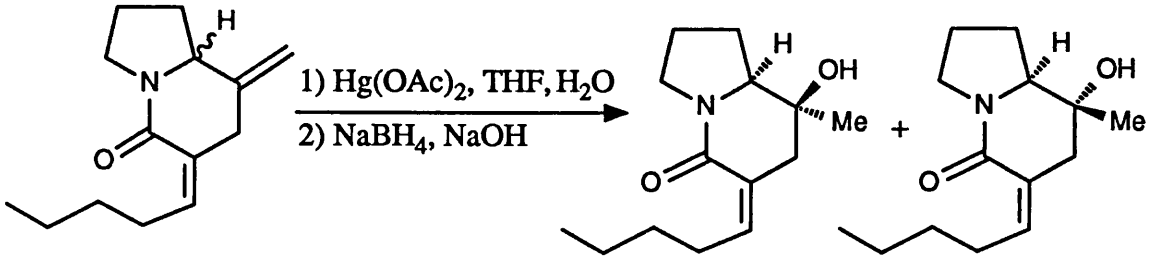
To investigate the possibility of enelactam isomerisation from the Z-geometry to the E-isomer, Z-(**195**) was treated with excess potassium hydroxide in refluxing methanol for 2h. Under these conditions, no equilibration to E-(**195**) was observed and the Z-enelactam could be cleanly recovered.

The role of the tertiary hydroxyl group in influencing the stereochemical outcome of the aldol reaction was examined by carrying out an aldol/elimination sequence with the optically impure unsaturated lactam (**77**)/*ent*-(**77**) (Scheme 158). Combination with pentanal as described previously, afforded a mixture of four aldol products with one major aldol adduct (**196d**) readily separable from the other three. Mesylation of the secondary hydroxyl followed by base-induced elimination generated the two enelactams Z- and E-(**197**) in a ratio indistinguishable from that achieved with the hydroxylactam. Two possible conclusions may be drawn from this: either the tertiary hydroxyl functionality has no influence on the aldol reaction of (**75a**) or its effect is counter-balanced by the change in the geometry of the bicyclic system as the hybridisation at C8 is altered.



E-(**197**)

E-(**195**)
98%



Z-(**197**)

Z-(**195**)

5 : 1

74%

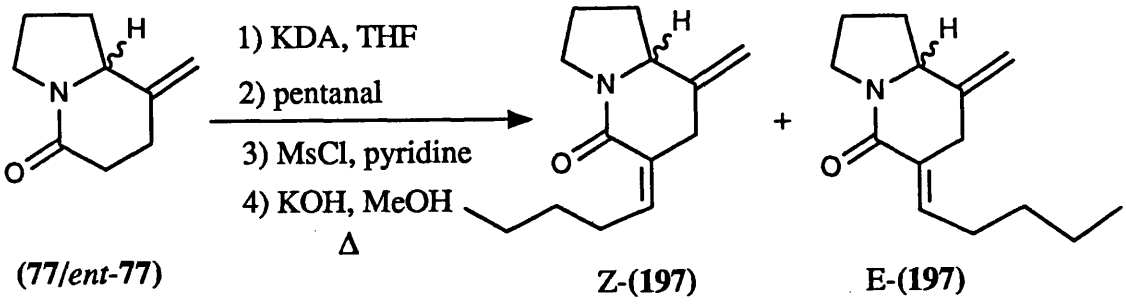
Scheme 159

The stereochemistry of the products obtained were assigned on a similar basis as described for **(195)**. Nonetheless, it was considered necessary to correlate Z- and E-**(197)** with the corresponding hydrated analogues by application of the hydroxymercuration/reduction procedure employed for the conversion of **(77)** to **(75a)** (Scheme 159).

Selective hydration of the C8-methylene double bond in E-**(197)** proceeded smoothly to provide E-**(195)** in high yield with no significant degree of C8-epimer formation. Under similar conditions, Z-**(197)** led to the isolation of a 5:1 mixture of C8-epimers, which could not be readily separated. The reduced stereoselectivity observed in this transformation compared with the hydration of **(77)** may be explained by the presence of an additional sp^2 centre at C6 which would tend to flatten the bicyclic system and so reduce the bias for attack by water at the β-face.

The high selectivity observed in the hydration of E-**(197)** is more difficult to rationalise, since this too includes an additional sp^2 centre at C6. It would appear, therefore, that the *n*-butyl side chain might act as a shield, preventing attack by water on the α-face of the double bond.

The spectral data of the major products obtained from these hydration experiments indicate that the stereochemical assignments made for Z- and E-**(197)** were indeed consistent with those of the hydrated series.


1) KDA, THF
2) pentanal
3) MsCl, pyridine
4) KOH, MeOH
Δ
(77/ent-77)
Z-(197)
E-(197)
1 : 1.5 kinetic
1 : 1.8 thermodynamic

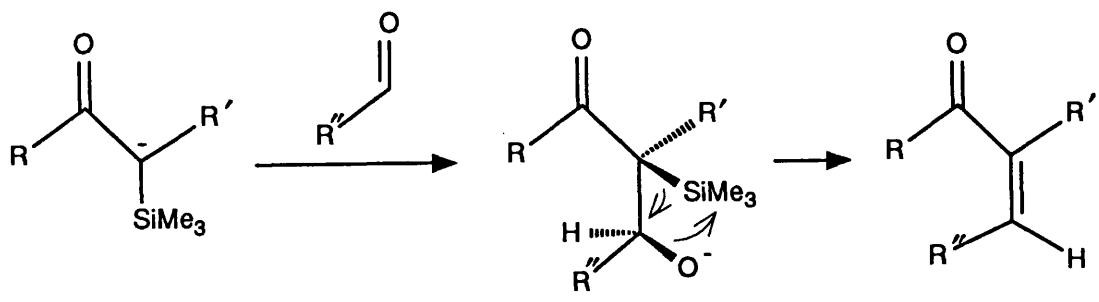
Scheme 160

The stereochemical course of aldol reactions has been shown, in a number of cases, to be dependent on the mode of quenching[176] and the particular metal cation present in the reaction medium.[179] The importance of these two factors were investigated within the context of the aldol condensation between the optically impure unsaturated lactam (**77**/*ent*-**77**) and pentanal.

Addition of a solution of potassium hexamethyldisilazide in toluene to the unsaturated lactam in THF, followed by addition of pentanal resulted in no observable reaction with the lactam substrate being cleanly recovered from the reaction mixture. However, when the sterically less hindered base potassium diisopropylamide (KDA) was used,[180] successful aldol formation was achieved. One half of the reaction mixture was quenched with excess glacial acetic acid at -78°C, 30s after the addition of the aldehyde (kinetic quench). The remainder of the reaction mixture was allowed to warm to room temperature prior to the addition of acetic acid (thermodynamic quench) (Scheme 160).

Both sets of aldol products were then separately treated under the usual *anti*-elimination conditions to afford the E- and Z-enelactam products in overall 31% yield. The ratio of geometrical isomers appeared to be largely independent of the mode of quenching and varied little from the product distribution obtained using LDA as the base.

These results suggest that the choice of either Li^+ or K^+ as the metal counterion has minimal influence on the stereochemical outcome of the aldol reaction. The conclusions to be drawn from the quenching experiments are less clear cut and do not necessarily suggest similar aldol stereochemical pathways under kinetic and equilibrating conditions. The similarity in Z/E selectivity following elimination could be a consequence of very rapid equilibration of the aldol adducts at -78°C, thus precluding a kinetic quench. Alternatively, very slow equilibration of the aldols at room temperature would mean that both reactions were performed under kinetic conditions. A final possibility that cannot be ruled out is that the *anti*-elimination conditions do not result in a stereospecific transformation and that the product ratio of enelactams does not strictly represent the distribution of aldol adducts (*vide infra*). The use of similar mesylation/base-mediated elimination conditions to assign aldol stereochemistry on the basis of subsequent double bond stereochemistry has, however, been an important tool in the structural determination of β-hydroxy carbonyl systems.[181]



(198)

Scheme 161

2.9(iii) Aldol/*Syn*-Elimination

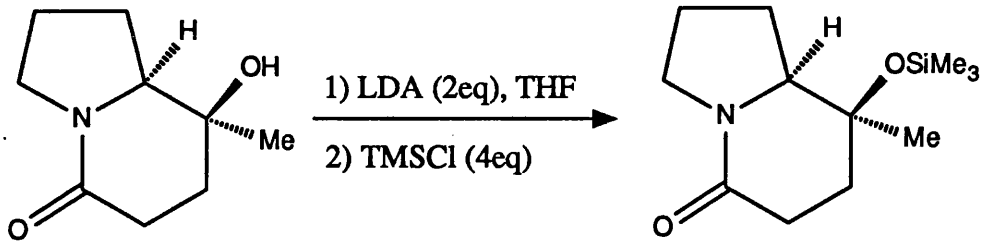
In the light of unsuccessful attempts to influence aldol stereochemistry prior to *anti*-elimination, it was proposed to seek a stereospecific *syn*-aldol elimination procedure in an effort to reverse the Z:E-enelactam selectivities that had been observed.

The Peterson reaction,[182] involving the condensation of the enolate of an α-silylcarbonyl compound with an aldehyde, is believed to proceed *via* an intermediate of the type **(198)** (Scheme 161), which undergoes *syn*-elimination to afford the unsaturated product. It was proposed that a similar procedure, applied to an α-silylated bicyclic lactam in combination with pentanal, would result in Z-enelactam formation. Peterson reactions involving α-silyl-*N*,*N*-dialkylamides and β-lactams have been reported by Evans[183] and Shibuya[184] respectively. A related approach has been employed by Matsui in the stereoselective synthesis of α-alkylidene lactones[185].

α-Silylation of carbonyl compounds is often complicated by competition between *O*- and *C*- silylation. Larson[186] has carried out a comprehensive investigation into the regioselectivity of silylation of lactones and its dependence on ring size. It was discovered that γ-lactones result in *C*-silylation whereas δ-valerolactone and ϵ-caprolatone underwent *O*-silylation.

Analogous studies have been carried out on *N*,*N*-disubstituted lactams in which it was found that even for six-membered rings, the *C*-silylated product was thermodynamically favoured with respect to the *O*-silyl compound.[187] This was attributed to the stabilising amide resonance interaction which is absent from the *O*-silylated products.

Scheme 162 illustrates the unsuccessful bid to effect *C*-silylation of the hydroxylactam **(75a)**. Rapid addition of excess TMSCl (purified according to Evans[183]) to the dianion of **(75a)** resulted in the isolation of **(199)**, the product of silylation at the tertiary hydroxyl.

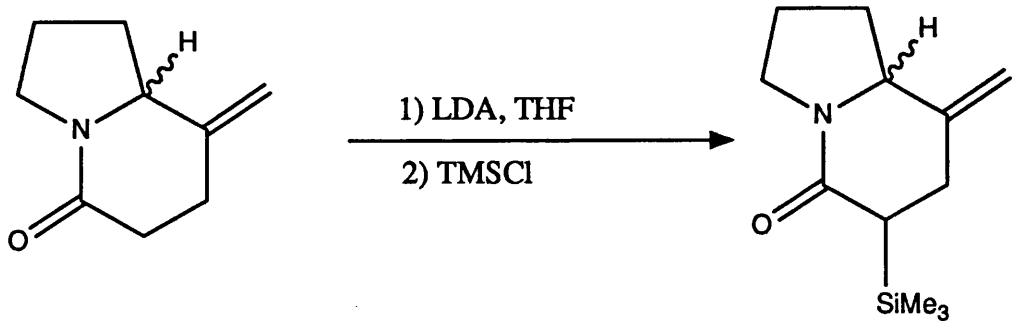


(75a) **(199)**

70%

Scheme 162

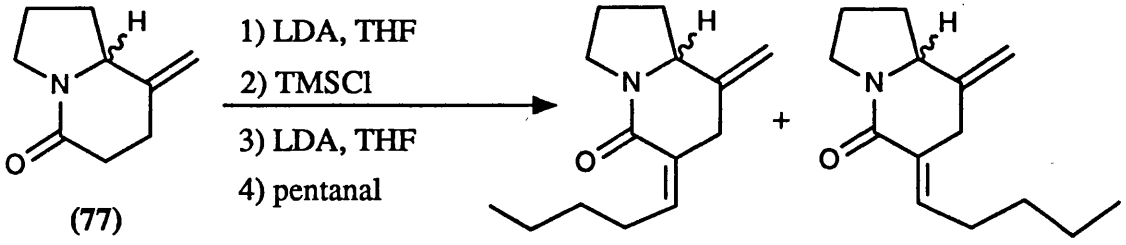
Attempts were made to isomerise this product to the desired α-silyllactam by treatment with *n*-butyllithium. 1,4-Silyl shifts have been observed by Evans[188] in which a stabilised alkoxide ion predominates in the equilibrium mixture. The chair-like conformation of the six-membered ring in **(199)** would, it was hoped, aid such a migration but in the event, no products of *C*-silylation were observed.



(77/*ent*-77)

(200)
28%

Scheme 163



(77)

Z-(197) E-(197)

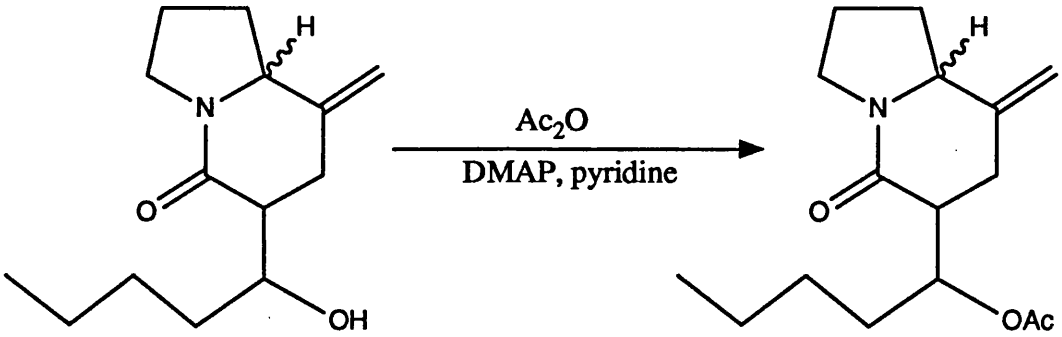
1 : 6

Scheme 164

To avoid the complication of the tertiary hydroxyl functionality, therefore, it was considered more convenient to use the unsaturated lactam (**77**) in this study (Scheme 163). The required product (**200**) was isolated, along with unchanged starting material, on combining the enolate anion of optically impure (**77**) with TMSCl. Since the silyl group in (**200**) was found to undergo rather rapid protonolysis, a "one-pot" approach was considered more appropriate (Scheme 164). Thus, *in situ* deprotonation of the α-silyllactam (**200**) followed by aldehyde addition at -78°C and warming to 0°C over 1h effected conversion to the enelactams (**197**) in a Z:E ratio of 1:6 as determined by proton NMR of the reaction mixture. Present also in the reaction mixture were the aldol products (**196**), reflecting incomplete α-silylation during the initial step. Although the yield of enelactams derived from the Peterson reaction remained undetermined, the reaction mixture was subjected to mesylation/elimination conditions to afford the products Z- and E-(**197**) in overall 56% yield.

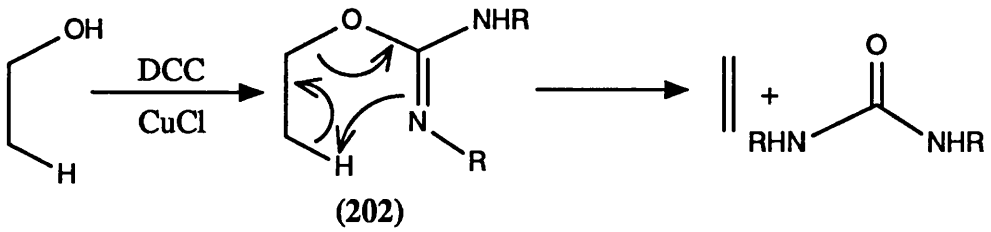
The disappointing selectivity in the Peterson reaction, resulting in a less favourable Z:E enelactam ratio, suggests an alteration in the stereochemical course of the initial addition of the enolate to the aldehyde. This could be a result of the presence of the bulky trimethylsilyl group adjacent to the reacting centre.[189]

Access to unsaturated systems in a stereodefined manner has been achieved previously by way of concerted, *syn*-pyrolysis of esters.[190] The viability of such an approach to the *syn*-elimination of the aldols **(196)** was assessed using the single aldol product **(196d)**, which on *anti*-elimination could be cleanly converted to E-**(197)**. Treatment with acetic anhydride in pyridine in the presence of (DMAP) afforded the corresponding acetate **(201)** in reasonable yield (Scheme 165).[191] No products of elimination could be detected, however, when a solution of **(201)** in *m*-xylene was heated to 200°C in a sealed tube over a 2 day period.



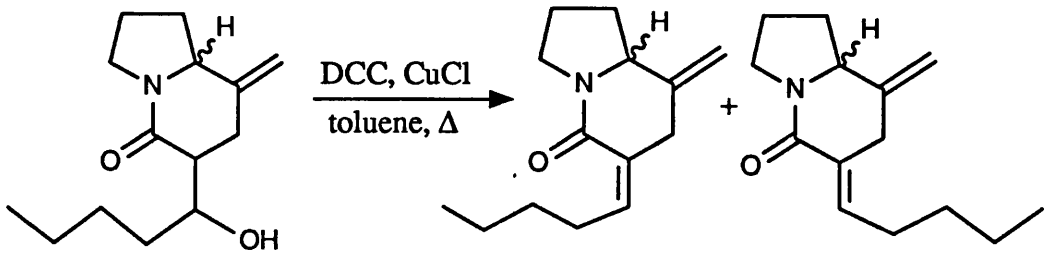
(196d) **(201)** 67%

Scheme 165



R=cyclohexyl

Scheme 166



(196a-d) **Z-(197)** **E-(197)**

1 : 1.2

69%

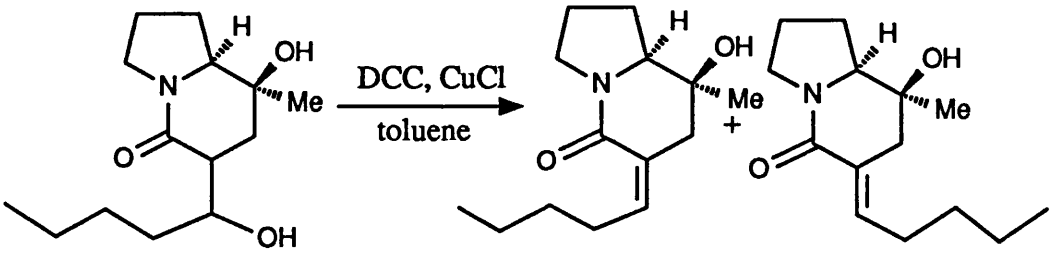
Scheme 167

It was decided to investigate a procedure for *syn*-aldol eliminations introduced by Corey[192] and later developed by Rouessac[193] employing dicyclohexylcarbodiimide (DCC) in the presence of copper(I) chloride. This transformation is believed to proceed *via* an initial carbamidate adduct of the type **(202)** (Scheme 166) which undergoes a concerted fragmentation. The role of the copper(I) chloride is, as yet, undefined although activation of DCC by copper(I) iodide has been recognised for some time.[194]

Addition of DCC (1 equivalent) and copper(I) chloride (catalytic) to the aldol mixture derived from the unsaturated lactam **(77)** and pentanal, effected very slow reaction in refluxing ether. However, after 15h in refluxing toluene, complete conversion to the Z- and E-enelactams was achieved in a ratio of 1:1.2 as indicated by proton NMR of the reaction mixture (Scheme 167). The products were obtained in a combined yield of 69% following chromatography.

When a similar sequence was repeated in the presence of copper(II) chloride as opposed to the copper(I) salt,[195] the only product obtained was the E-enelactam, isolated in 81% yield. This observation suggests that the mechanistic pathway of the DCC-mediated elimination is highly dependent on the choice of copper catalyst.

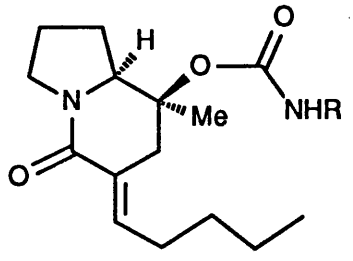
Complications arose when the *syn*-elimination procedure was applied to the aldol mixture (**203a-d**) derived from the hydroxylactam (**75a**). Treatment with stoichiometric DCC in refluxing toluene, in the presence of copper(I) chloride lead to partial reaction, with complete disappearance of one of the aldol components. Three new compounds were formed under these conditions; the Z- and E-enelactams, in similar proportions (combined yield 59%) together with a third component (**204**), which was assigned the structure shown in Scheme 168 on the basis of proton NMR analysis and by analogy with subsequent observations (section 2.10(iv)). This third product was formed only after prolonged heating in toluene and it is proposed that following initial addition of an appropriate aldol component to DCC to form the carbamidate, subsequent concerted *syn*-elimination is disfavoured by steric congestion between the *n*-butyl chain and the neighbouring carbonyl group.



(**203a-d**) Z-(**195**) E-(**195**)

1.1 : 1

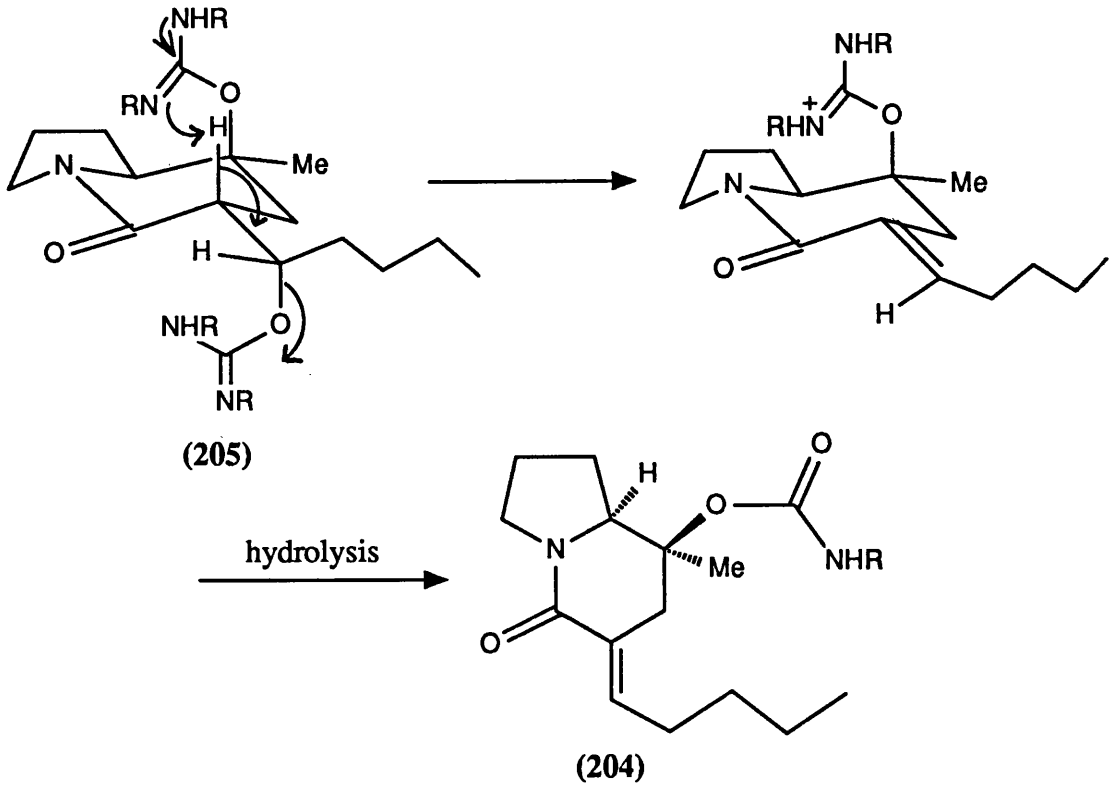
+



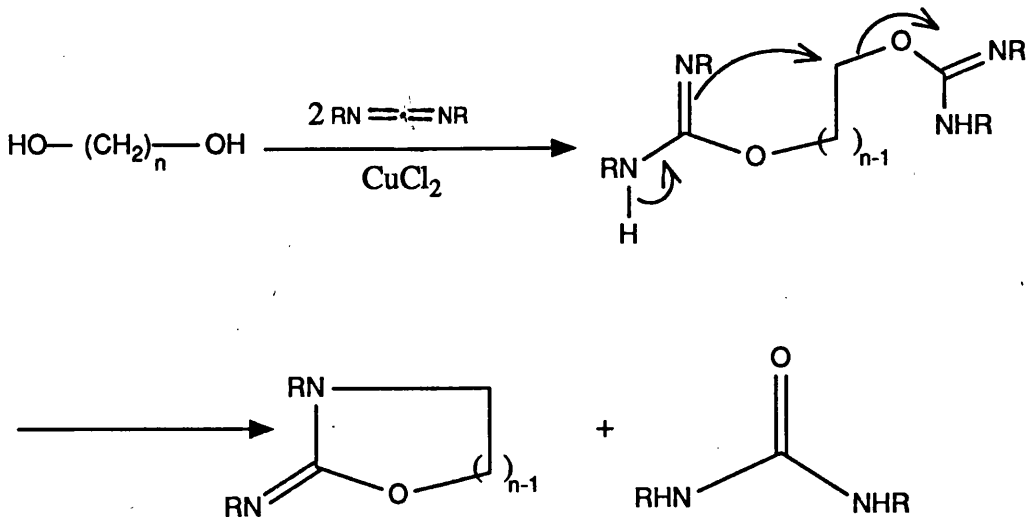
R=cyclohexyl

(**204**)

Scheme 168



Scheme 169

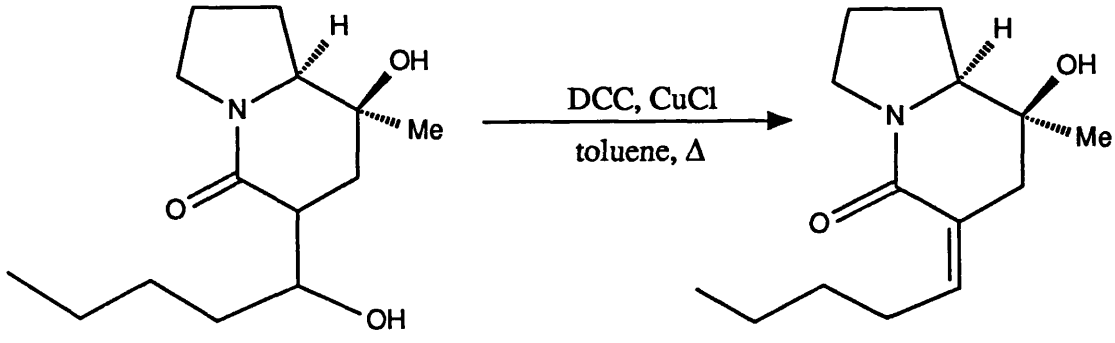


Scheme 170

However, after extended exposure to DCC, the tertiary alcohol functionality at C8 of the indolizidine skeleton could also undergo addition to DCC forming the bis-carbamidate (**205**).

The bis-adduct is now suitably disposed to effect an *anti*-displacement as indicated in Scheme 169 which, following aqueous work-up, would afford the carbamate (**204**). An analogous process has been observed by Schmidt[196] in which DCC reacted with diols to form bis-carbamidates leading to 1,3-oxazolidines (n=2) or 1,3-oxazolines (n=3) following nucleophilic displacement (Scheme 170). It should be stressed that no stereochemical assignments for the individual aldols have been ascertained and that the mechanism proposed in Scheme 169 is merely conjecture. Further support for the structure of (**204**) was, however, provided by basic hydrolysis (potassium hydroxide/methanol/reflux) which led directly to the E-enelactam E-(**195**).

It would appear, therefore, that the DCC-mediated *syn*-elimination is unsuitable for the combined aldol mixture (**203a-d**). However, since a significant quantity of the desired Z-enelactam was formed using this procedure, it was decided to separate the aldol adducts prior to elimination and to subject each to the *syn*-elimination conditions individually.



(203d)

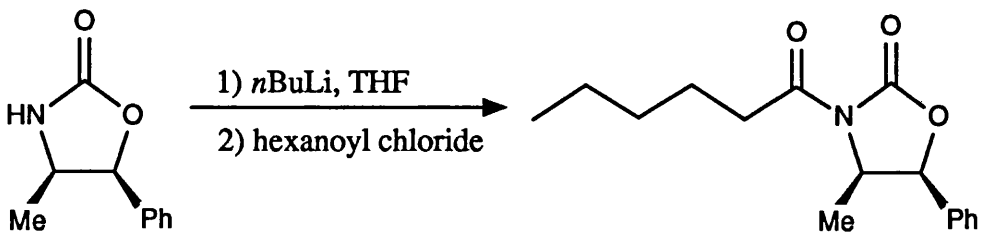
Z-(195)
78%

Scheme 171

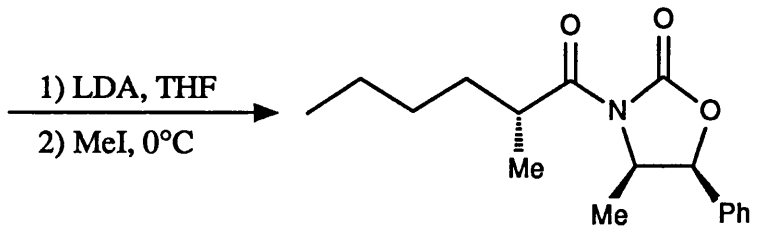
In practice, one aldol component **(203d)** was separable from the other three (203a-c) by column chromatography, and this underwent smooth conversion to the Z-enelactam Z-**(195)** after heating with stoichiometric copper(I) chloride and DCC in toluene for 4h (Scheme 171). However, when the remaining mixture of aldol adducts **(203a-c)** was treated under similar conditions, no Z-enelactam formation was detected after 4h and proton NMR analysis of the crude reaction mixture indicated the presence of E-enelactam along with unchanged aldols.

The convenient use of DCC for the efficient conversion of the single aldol product **(203d)** to the desired Z-enelactam was a technique that translated well to the preparation of the Z-enelactam Z-**(74)** bearing the chiral alkylidene residue (section 2.10). Equally relevant to the more complex system, however, were the doubts raised concerning non-stereospecificity of the elimination process when applied to the aldol mixture as a whole.

The following section describes aldol/elimination sequences involving the chiral aldehyde **(76)** required to complete the total synthesis of **(7)** and how this series of experiments puts into question the stereospecificity of both the *syn*- and *anti*-elimination procedures employed.

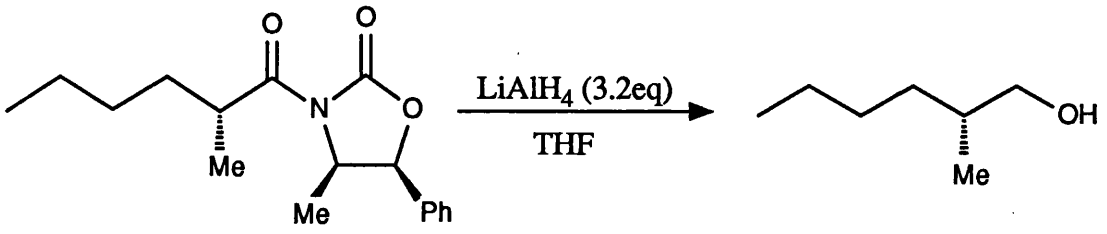


(206)
91%



(207)
59%

Scheme 172



(207) **(208)**
75%

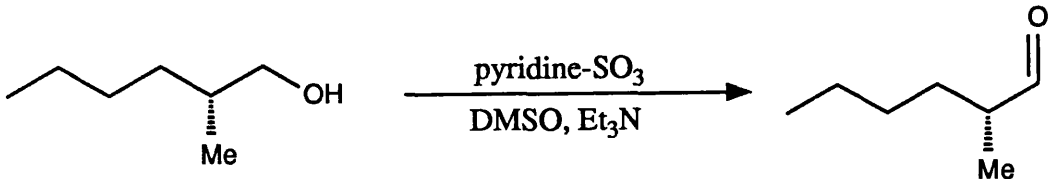
Scheme 173

2.10 Use of the Chiral Aldehyde in the Aldol/Elimination Sequence

2.10(i) Synthesis of (R)-2-methylhexanal.

The retrosynthetic analysis (Scheme 56) for the target molecule pumiliotoxin 251D requires the participation of the chiral aldehyde (R)-2-methylhexanal **(76)** in an aldol/elimination sequence with the optically pure hydroxy lactam **(75a)**. Access to **(76)** from the corresponding alcohol reduces the problem to the synthesis of (R)-2-methylhexanol **(208)** which has been synthesised by Mori[197] in enantiomerically pure form from methyl β-hydroxyisobutyrate.

For the purposes of the present synthesis, however, it was considered more expedient to employ the methodology developed by Evans[198] for the stereoselective alkylation of chiral *N*-acyl-2-oxazolidinones. Schemes 172 and 173 illustrate how this procedure was successfully applied to the synthesis of (R)-2-methylhexanol from hexanoyl chloride in overall 40% yield. Successive treatment of 4-methyl-5-phenyl-2-oxazolidinone[199] with *n*-butyllithium and hexanoyl chloride furnished **(206)** in an excellent recrystallised yield. This underwent highly stereoselective methylation to afford **(207)** as a single diastereoisomer in 59% yield following chromatography. Reduction proceeded equally smoothly to provide the alcohol R-**(208)**; $[\alpha]_D^{18}$ +8.1° (c 0.67, Et_2O); +9.5° (c 14.2, Et_2O) [Lit[156] $[\alpha]_D^{21}$ +13.6° (c 21.5, Et_2O)].



(208) (76)

Scheme 174

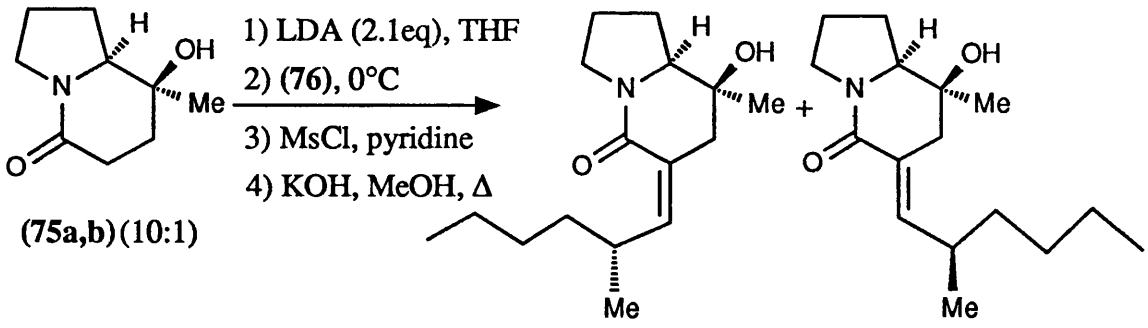
More rigorous evaluation of the optical purity of the alcohol was carried out by formation of the (R)-MTPA ester[169] and comparison of the proton NMR spectrum with that obtained from the racemic alcohol.[200] The enantiomeric purity of R-(**208**) was determined to be in excess of 95% by this method.

Oxidation to the required aldehyde (**76**) was achieved using pyridine-sulphur trioxide complex in DMSO (Scheme 174).[129] Conversion occurred with no significant racemisation as evidenced by re-reduction with lithium aluminium hydride and analysis of the corresponding MTPA ester by proton NMR. The aldehyde prepared by this method was used in the subsequent aldol reactions without further purification or characterisation.

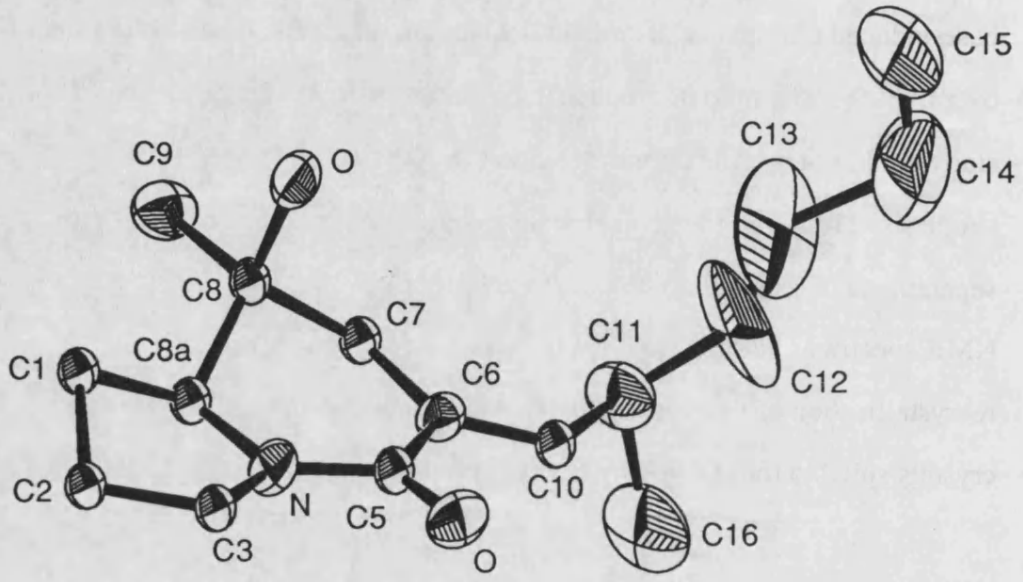
As described previously (section 2.8), the optically pure hydroxylactam (**75a**) could be isolated in diastereomerically pure form by recrystallisation of the 10:1 mixture of C8 epimers obtained during the hydroxymercuration step. It was more expedient however, to use the 10:1 diastereomeric mixture, obtained in 95% yield from (**77**), directly in the addition to the optically pure aldehyde. Removal of the minor components was then effected at a later stage. Adopting this protocol resulted in higher overall yields of enelactams following elimination and circumvented the difficulties encountered with recrystallisation of the optically pure hydroxylactam.

2.10(ii) Aldol/*Anti*-Elimination

The aldol/*anti*-elimination sequence, employed for the model system described earlier, was applied to the optically pure hydroxylactam and the chiral aldehyde **(76)** as shown in Scheme 175. Thus, treatment of the aldol mixture resulting from the addition of the aldehyde to the lithio-dianion of **(75a,b)** with methanesulphonyl chloride in pyridine, followed by base-induced elimination afforded a 1:6 mixture of Z- and E-enelactams in overall 39%. The ratio of products indicated that the results of the model study could not be directly translated to the system aimed at the total synthesis. However, the geometrical isomers were, once again, readily separable and assignments could be established on the basis of their proton NMR spectra as before. Both enelactams were crystalline solids and recrystallisation of the E-isomer from dichloromethane/petrol furnished crystals suitable for analysis by X-ray crystallography (Figure 8).



Scheme 175



ORTEP diagram of E-(**74**).

Thermal ellipsoids represent 30% probability.

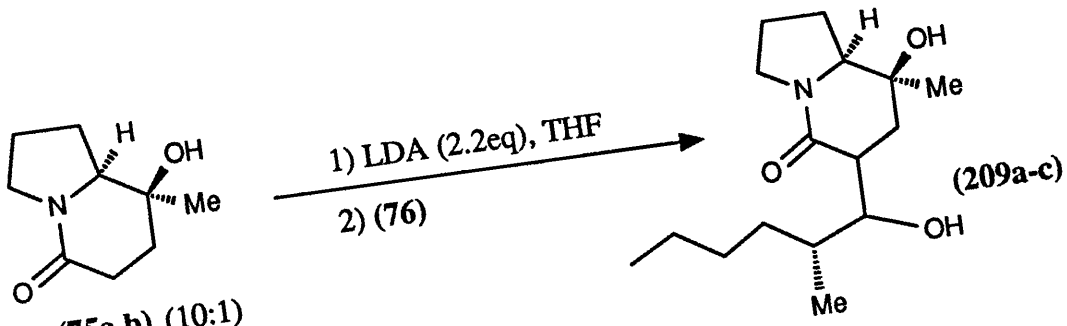
Labelling according to indolizidine numbering system.

Figure 8

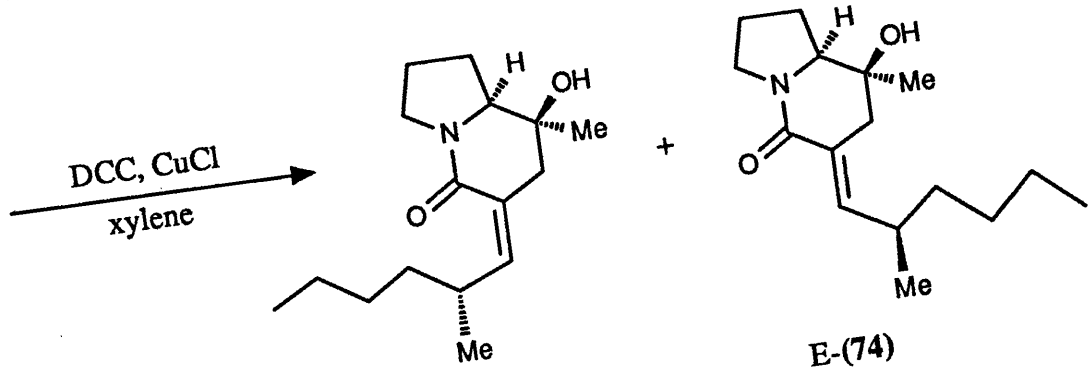
The structural determination at this stage served to confirm three stereochemical assignments that were vital for the purposes of the total synthesis. The absolute stereochemistry at C11, derived from (R)-methylhexanol, is established and so allows assignment of (S)-configuration at C8a, the stereochemistry required for the pumiliotoxin A family. This demonstrates, unequivocally, that the correct diastereoisomer of the acrylate ester **(144b)** resulting from palladium(II)-mediated cyclisation, had indeed been selected for further elaboration.

Secondly, the (S)-stereochemistry at C8 verifies that the hydroxyl group has been introduced with the required axial orientation.

Thirdly, the double bond (C6-C10) is clearly shown to have E geometry, as assigned on the basis of the proton NMR spectrum. This combined stereochemical information is equally relevant to the Z-enelactam and so provides unambiguous corroboration for its proposed structure.



(75a,b) (10:1)



Z-(74) E-(74)

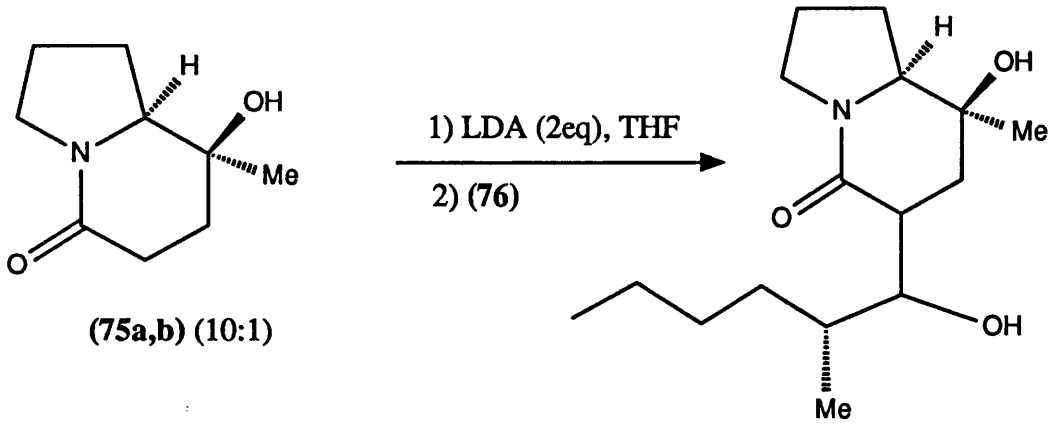
1 : 1.4

29%

Scheme 176

2.10(iii) Aldol/*Syn*-Elimination

On the basis of the poor Z/E-enelactam selectivity following *anti*-elimination, it was envisaged that an aldol/*syn*-elimination sequence would furnish the required Z-enelactam as the major product. As with the model system, however, problems arose when the DCC-mediated *syn*-elimination was attempted on the combined aldol mixture (Scheme 176). Aldol condensation of **(75a,b)** (10:1 mixture) with the aldehyde **(76)** afforded three major aldol components **(209a-c)** which were used without further purification in the elimination step. Addition of stoichiometric DCC and copper(I) chloride to a solution of the aldol in *m*-xylene afforded, after 24h reflux, the Z- and E-enelactams in a ratio of 1:1.4 and a combined yield of 29% from the hydroxylactam **(75a,b)**. This Z:E ratio does not reflect the Z:E ratio obtained in the *anti*-elimination and suggests, therefore, that one or both of these processes is occurring in a non-stereospecific manner. Further evidence for this was obtained when eliminations were carried out on separated aldols in an attempt to optimise the transformation of the hydroxylactam **(75a)** to the Z-enelactam Z-**(74)**.



(75a,b) (10:1)

(209a-c) 69%

a+b:c 1.6:1

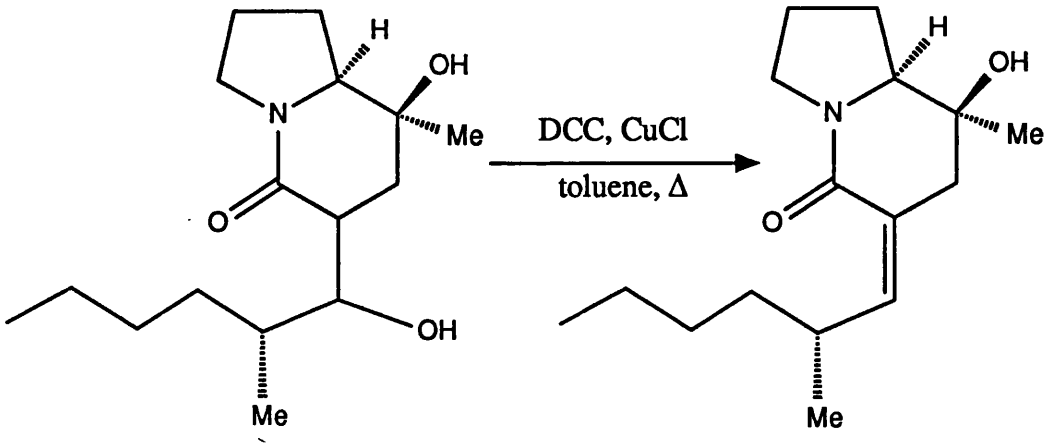
Scheme 177

2.10(iv) Optimisation of Aldol/Elimination

The mixture of aldol adducts **(209a-c)**, obtained in 69% purified yield from the 10:1 mixture **(75a,b)** of hydroxylactams, comprised three components, one of which,**(209c)**, was readily separable from **(209a,b)** The proportion of each is shown in Scheme 177.

No attempt has been made to elucidate the stereochemistry at C6 and C10 of the aldol adducts although some distinction may be observed in the coupling pattern of the C6 proton in the NMR spectra of the adducts. Thus, whereas for **(209a,b)**, the proton attached to C6 is observed to couple with the neighbouring protons at C7 with *J* values of 11Hz and 8Hz, for **(209c)**, the corresponding *J* values are 11Hz and 3Hz.

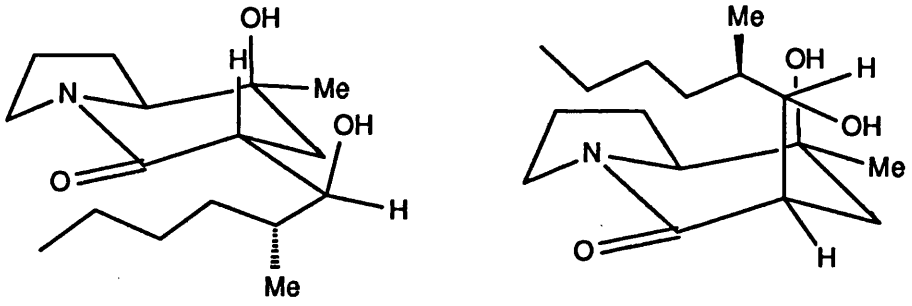
Addition of DCC (1.2 equivalents) and stoichiometric copper(I) chloride to a solution of the single aldol adduct **(209c)** in toluene, followed by heating at reflux for 24h, effected complete conversion to the Z-enelactam Z-**(74)** in 98% purified yield (Scheme 178).



(209c) Z-**(74)** 98%

Scheme 178

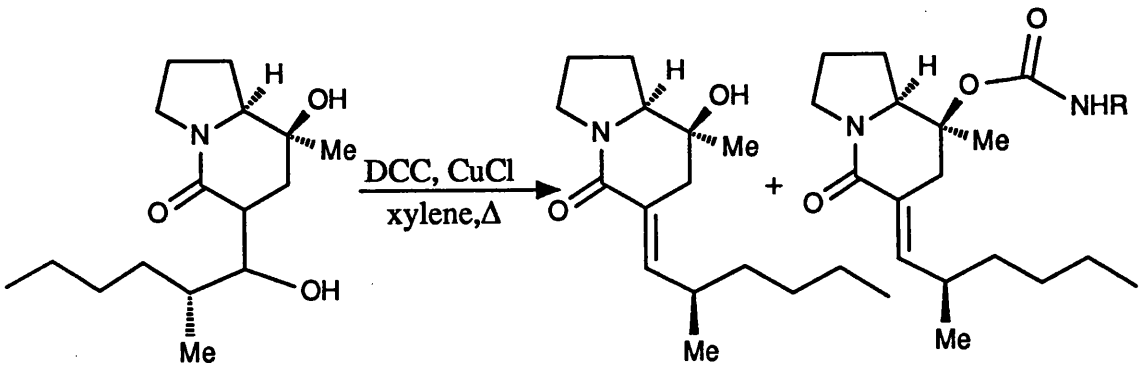
With the assumption that this proceeds *via* a *syn*-elimination, the stereochemistry of aldol **(209c)** may be assigned as either **A** or **B** as shown in Figure 9. Of these two structures, **B** might be expected to undergo more facile *syn*-elimination; steric strain released on converting C6 from sp^3 hybridisation with a bulky axial group to sp^2 would be expected to provide a suitable driving force.[201] Aldol **A**, however, would need to adopt an unfavourable conformation to effect *syn*-elimination, in which the side chain and the carbonyl group are in close proximity to one another.



(A) **(B)**

Figure 9

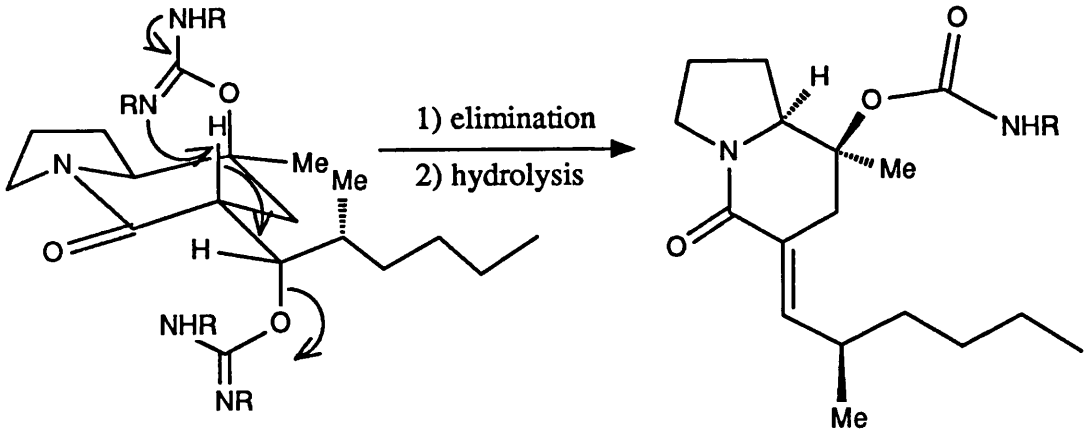
Further support for these structural assignments are provided by the results of subjecting the aldol mixture **(209a,b)** to similar *syn*-elimination conditions.



(209a,b) **E-(74)** **(210)**

R=cyclohexyl

Scheme 179



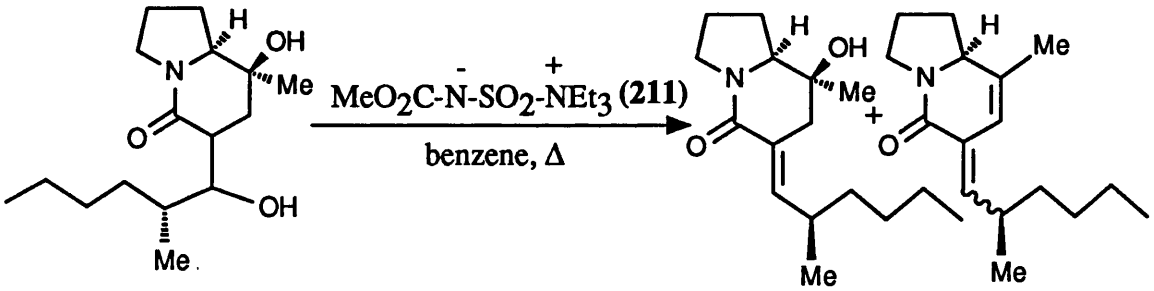
(210)

Scheme 180

Thus, treatment of a solution of the aldol mixture in *m*-xylene with stoichiometric DCC and copper(I) chloride effected incomplete conversion to E-**(74)** with no trace of the Z-enelactam after 24h. However, addition of excess DCC and continued heating induced the appearance of a second component **(210)** (Scheme 179). The structure of **(210)** was assigned on the basis of spectral data, in particular a molecular ion peak at 391 in the C.I. mass spectrum. Formation of this carbamate may be rationalised on a similar basis as described in section 2.9(iii) in which initial bis-carbamidate formation is followed by an *anti*-elimination sequence to afford the E-enelactam (Scheme 180). Such a mechanism would require the participation of aldol **A** which is consistent with the assignment of structure **B** to aldol **(209c)**.

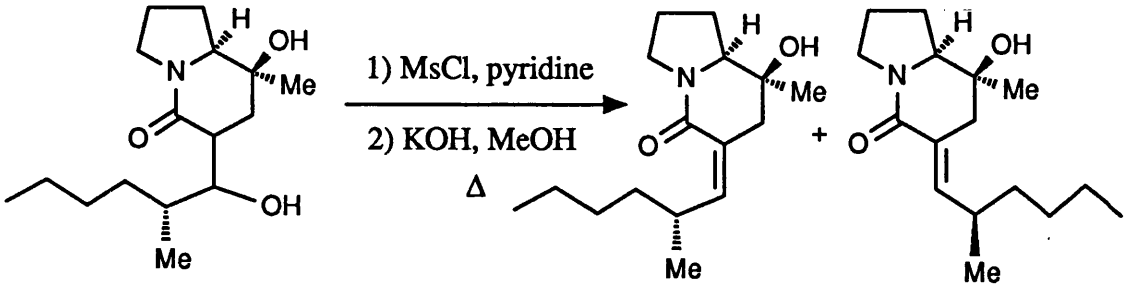
These proposals require that the six-membered ring portion of the indolizidine skeleton retains a chair-like conformation. In the absence of further evidence to support the assignments suggested, this rather speculative model should be treated as no more than a working hypothesis.

As a result of the difficulties experienced in applying the DCC-based *syn*-elimination procedure, an alternative method for effecting concerted alcohol eliminations was attempted. The Burgess reagent **(211)** is a common choice for effecting such transformations and was synthesised according to literature procedure.[202] Addition of 1 equivalent to a solution of the aldol mixture **(209a,b)** in refluxing benzene resulted in complete conversion to two products after 2h, neither of which were the desired Z-enelactam (Scheme 181). Along with the E-enelactam E-**(74)** was a second component, the structure of which was not determined unambiguously. However, an addition singlet in the proton NMR spectrum at 6.18 p.p.m. suggests a double elimination resulting in the structure shown. The shift of the vinylic proton attached to C10 (6.36 p.p.m.) does not allow unequivocal assignment of enelactam geometry.



(209a,b) Z-(74)

Scheme 181



(209a,b)

Z-(74) **E-(74)**

1 : 2.6

73%

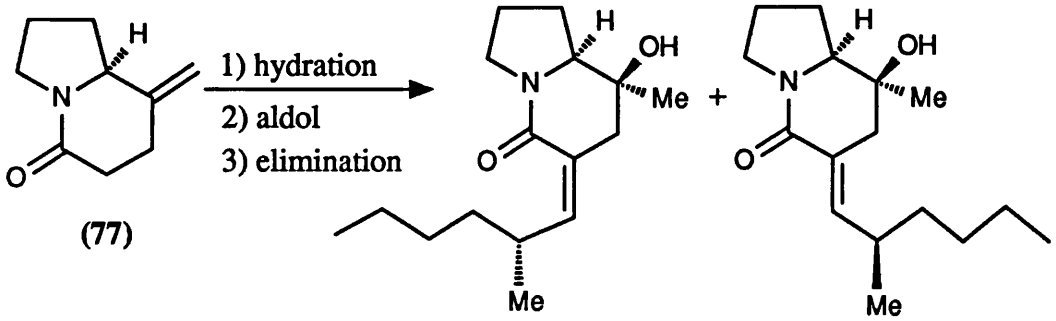
Scheme 182

At this stage, the effect of subjecting the aldol mixture **(209a,b)** to *anti*-elimination conditions was investigated, in terms of the distribution of Z- and E-enelactam products. During these experiments a number of different Z:E ratios were obtained, depending on the particular *anti*-elimination conditions employed. Such observations indicate a lack of stereospecificity in these transformations. Similar phenomena have been observed in other systems where conformations required for *anti*-elimination have been sterically disfavoured, resulting in alternative pathways e.g. E_1cB.[176,203] Selective mesylation of the aldol mixture **(209a,b)** afforded a 4:1 mixture which was purified by chromatography. This was dissolved in methanol, excess potassium hydroxide added and the reaction gradually warmed to reflux over 1h and continued for a further 2h. Proton NMR analysis of the reaction mixture following work-up indicated a Z:E ratio of 1:2.6 and the two products were isolated in a combined yield of 73% over the two steps (Scheme 182). When a similar sequence was applied to the same aldol mixture, with no purification of the intermediate mesylate and a reaction temperature of 60°C prior to the addition of potassium hydroxide, the ratio of E:Z enelactams was 4:1 obtained in an isolated yield of 70%. The product ratio became 5.4:1 (E:Z) when the mesylate elimination was carried out overnight at room temperature.

Changing the base also had an influence on the stereochemical course of the elimination and the use of sodium bicarbonate in refluxing methanol resulted in an E:Z ratio of 4:1. Triethylamine in either methanol or THF was unsuccessful in effecting elimination. An improvement in the efficiency of the leaving group was envisaged to provide a solution to the poor stereocontrol in the elimination step, if competing E_1cB pathways were in operation. Thus, triflic anhydride was added to the aldol mixture **(209a,b)** in the presence of DMAP. However, no evidence for the formation of the intermediate triflate or the desired elimination products could be discerned and components apparent in the proton NMR spectrum of the reaction mixture remained unidentified.

In conclusion, therefore, the most favourable *anti*-elimination sequence for the aldol mixture **(209a,b)**, in terms of Z:E ratio is that illustrated in Scheme 182. An unsuccessful attempt to alter the ratio of aldol adducts by use of the zinc enolate of **(75a)** in the aldol reaction[204] resulted in no aldol formation with only unchanged starting material being recovered from the reaction mixture.

Scheme 183 summarises the efficiency of the combined transformations involving hydration of the unsaturated lactam (**77**) and introduction of the Z-alkylidene side chain, necessary for the total synthesis of (**7**). It is evident that the aldol/elimination sequence has been reasonably successful in incorporating the side chain with respect to both chemical yield and stereoselectivity.



(77)

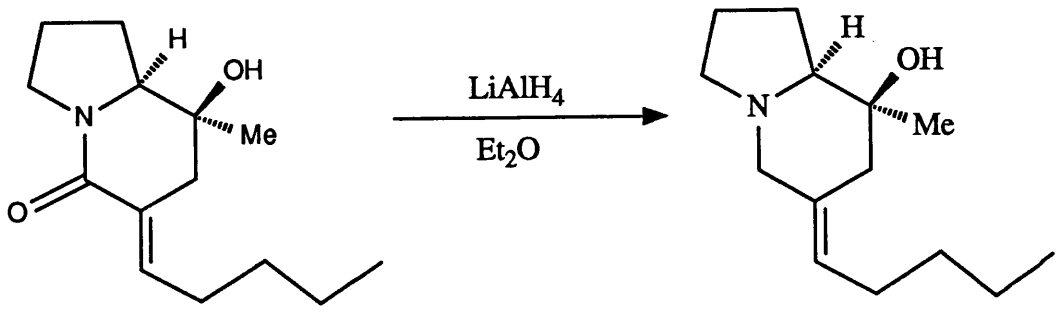
Z-(74) E-(74)

1.6 : 1

54%

Scheme 183

The remaining transformation required to complete the synthesis was carbonyl reduction of the Z-enelactam and the next section describes the factors to be considered in such a process and how these were accommodated.



E-(195) (31)

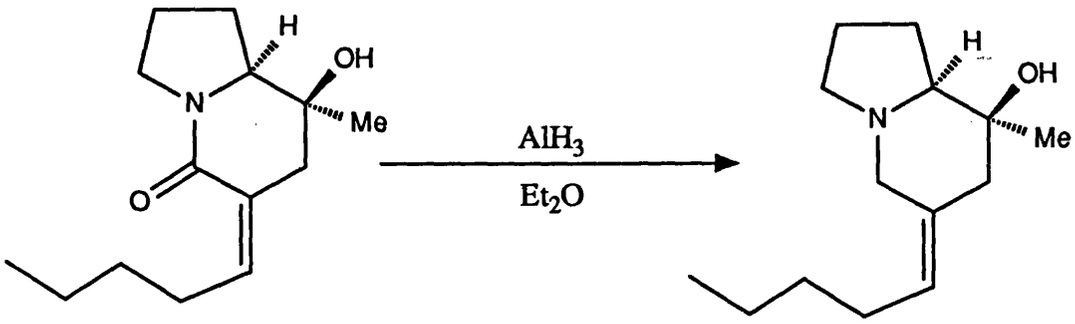
Scheme 184

2.11 Completion of the Total Synthesis

2.11(i) Model Studies on Carbonyl Reduction

In section 2.9(ii) it was described how conversion of the Z- and E-enelactams **(195)** to the pumiliotoxin analogues **(32)** and **(31)** was achieved using DiBAl in ether. In the case of Z-enelactam, a degree of Z/E double bond isomerisation was observed and the product comprised of mixture of **(32)** and **(31)**. It was necessary, therefore, to seek a reducing agent that would not introduce such difficulties.

Lithium aluminium hydride had been shown to effect conversion of the E-enelactam E-**(195)** to **(31)** in poor yield (Scheme 184). However, this did not translate directly to the more complex Z-enelactam required for the total synthesis since addition of lithium aluminium hydride to Z-**(195)** in THF effected 1,4 reduction of the α,β-unsaturated system prior to carbonyl reduction. The proton NMR spectrum of the reaction mixture indicated the complete absence of olefinic peaks, highlighting the reactive nature of the exocyclic Z-alkenyl system. Thus, a reagent that effected clean 1,2-reduction with no double bond isomerisation was required. The procedure of Borch[205] for the reduction of tertiary amides *via* the imino ether fluoroborate failed to effect any reaction with the unsaturated Z-enelactam Z-**(195)** and only starting material was recovered. Other reagents, such as diborane, which are commonly used to reduce amides to amines, were not expected to show the required selectivity for the lactam in the presence of the alkenyl functionality.



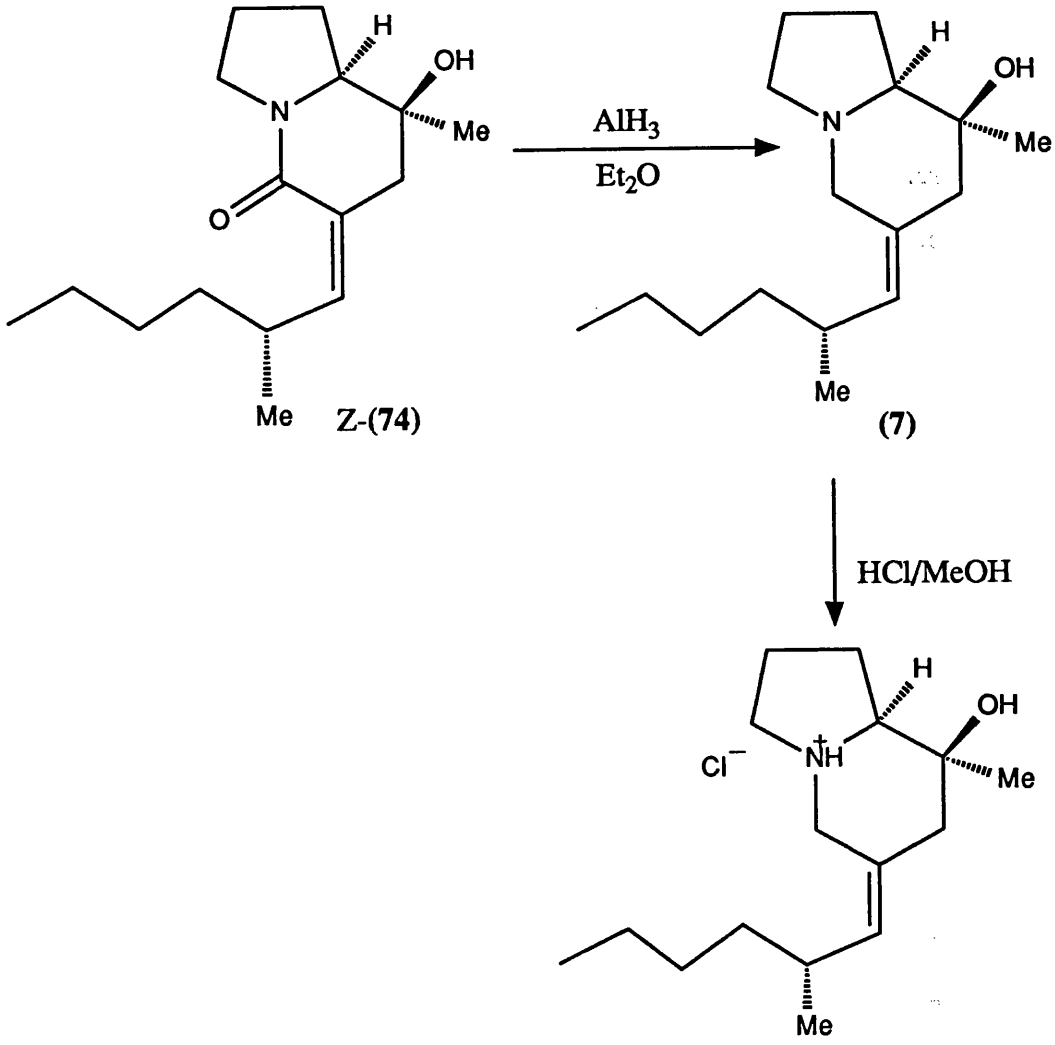
Z-(195) **(32)**

43%

Scheme 185

The use of aluminium hydride as a highly reactive carbonyl reducing agent has not become as widespread as that of the ubiquitous lithium aluminium hydride. In 1962, Jorgensen published a paper on the use of aluminium hydride as a selective carbonyl reducing agent for α,β-unsaturated carbonyl compounds.[206] The aluminium hydride was conveniently prepared as a ethereal solution, by the addition of 1 equivalent of aluminium chloride to a solution of 3 equivalents of lithium aluminium hydride in ether. The precipitated lithium chloride falls to the bottom of the reaction flask and the solution above may be used without filtration. This unique property of aluminium hydride as a selective reducing agent was later confirmed by Brown in a comprehensive study of its properties and uses.[207]

The successful reduction of the Z-enelactam Z-**(195)** to the pumiliotoxin analogue **(32)** previously synthesised is illustrated in Scheme 185. The product was the only component observed in the reaction mixture and was obtained in a moderate 43% yield following chromatography, reflecting the potentially volatile nature of the amine. It remained to demonstrate that the efficiency of this reagent with the model system was equally pertinent to the completion of the natural product synthesis.

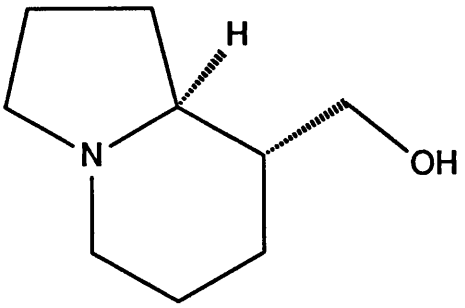

H
OH
N
Me
O
Me
Z-(74)
AlH3
Et2O
H
OH
N
Me
Me
(7)
HCl/MeOH
H
OH
Cl−
NH
Me
Me
(7)-HCl
67%

Scheme 186

2.11(ii) Isolation and Characterisation of Pumiliotoxin 251D

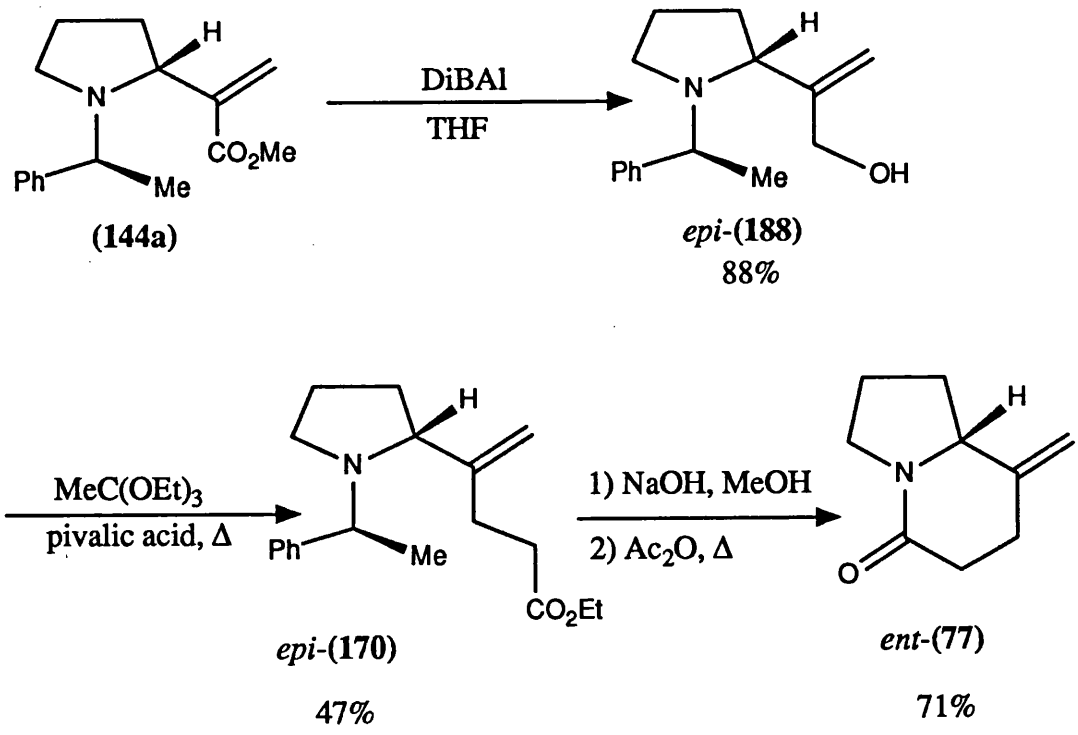
Scheme 186 illustrates how the addition of a solution of aluminium hydride to the Z-enelactam Z-(**74**) effected clean and rapid conversion to the target molecule, pumiliotoxin 251D. The amine was converted to the HCl salt and initially characterised as such, owing to the notorious volatility of the free base. The HCl salt was obtained in 67% yield and, along with the free base, exhibited identical spectral characteristics to those reported by Overman.[4d] Recrystallisation of the hydrochloride salt from petrol/ether furnished colourless crystals m.p. 188-189°C accompanied by sublimation. Determination of the melting point in an evacuated sealed capillary gave a melting point value of 200-201°C (lit. 206-206.5°C). The optical rotation was also obtained on a sample of the recrystallised hydrochloride salt. $[\alpha]_D^{20}$ +23.6° (c 0.11, MeOH); $[\alpha]^{20}_{546}$ +36.1° (c 0.11, MeOH). Lit[4d]: $[\alpha]_D^{21}$ +28.0° (c 0.62, MeOH); $[\alpha]_{546}^{25}$+ 32.0° (c.62, MeOH).
Thus, within the experimental errors inherent in the technique for determining optical rotation,[208] the values obtained compare favourably with those reported by Overman.

Similar reduction conditions were applied to the E-enelactam and proton NMR analysis of the corresponding hydrochloride salt clearly distinguished the E-alkylidene isomer of pumiliotoxin 251D from the natural product, thus ruling out any Z/E double bond isomerisation in the final step. The total synthesis described provides pumiliotoxin 251D in 9 steps from the allenic amine (**88**) and an overall yield of 6.3%. Its versatility derives from the ability to combine the hydroxy lactam (**75a**) with a range of chiral aldehydes in an aldol/elimination sequence and so providing, on carbonyl reduction, flexible access to a range of pumiliotoxin A alkaloids and analogues (see section 2.13).



(-)-(**212**)
tashiromine

Figure 10



(**144a**)

epi-(**188**)
88%

epi-(**170**)
47%

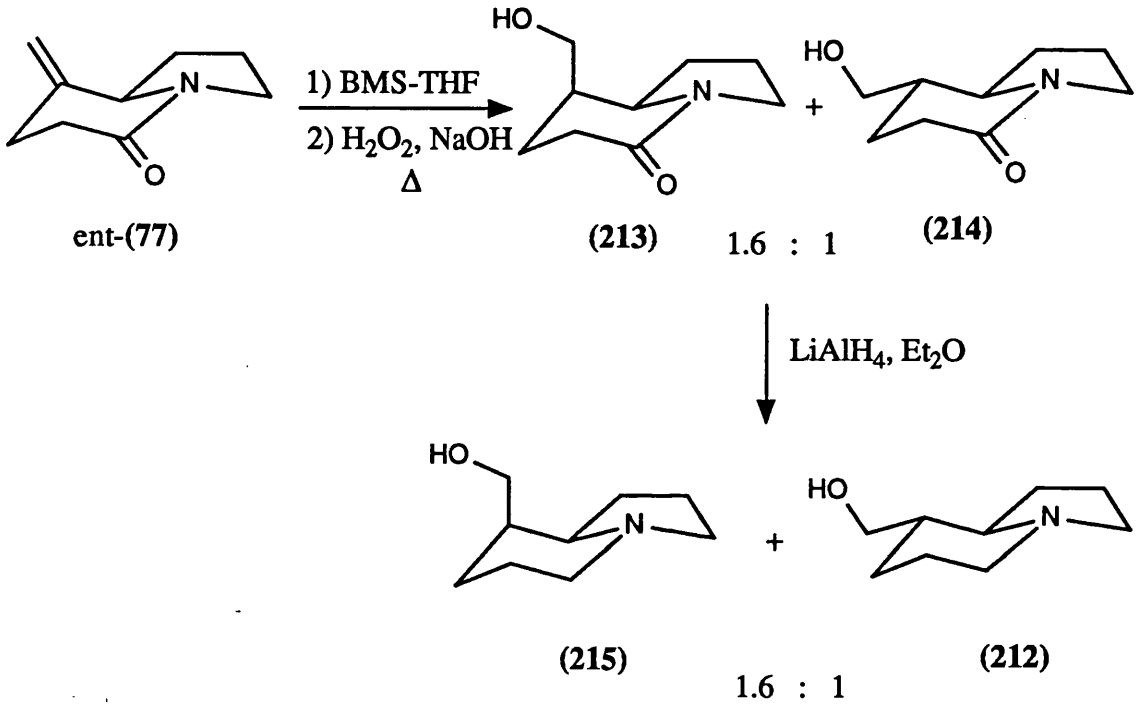
ent-(**77**)
71%

Scheme 187

2.12 A Synthesis of (+)-Tashiromine

During the course of this work, a new alkaloid, tashiromine, was isolated by a group of Japanese workers[209] and its structure is shown in Figure 10. The alkaloid is derived from the stems of *maackia tashiroi Leguminosae*, a deciduous shrub distributed widely in subtropical Asia and although the absolute stereochemistry of the natural product is not known, one enantiomer has recently been synthesised. The (8aS, 8R) enantiomer (based on indolizidine numbering) was accessed *via* alkylation of a chiral tin(II) enolate and has been shown to be laevorotatory.[210]

Its structural resemblance to the bicyclic lactams **(77)** and **(75a)** together with the fact that one diastereoisomer of the product of palladium(II)-mediated cyclisation **(144a)** had remained unused, prompted a brief investigation into its synthesis. Scheme 187 illustrates how the **(144a)** was converted to the (C8a R) unsaturated bicyclic lactam *ent*-**(77)** in 29% by employing the transformations used in the total synthesis of pumiliotoxin 251D.[211]

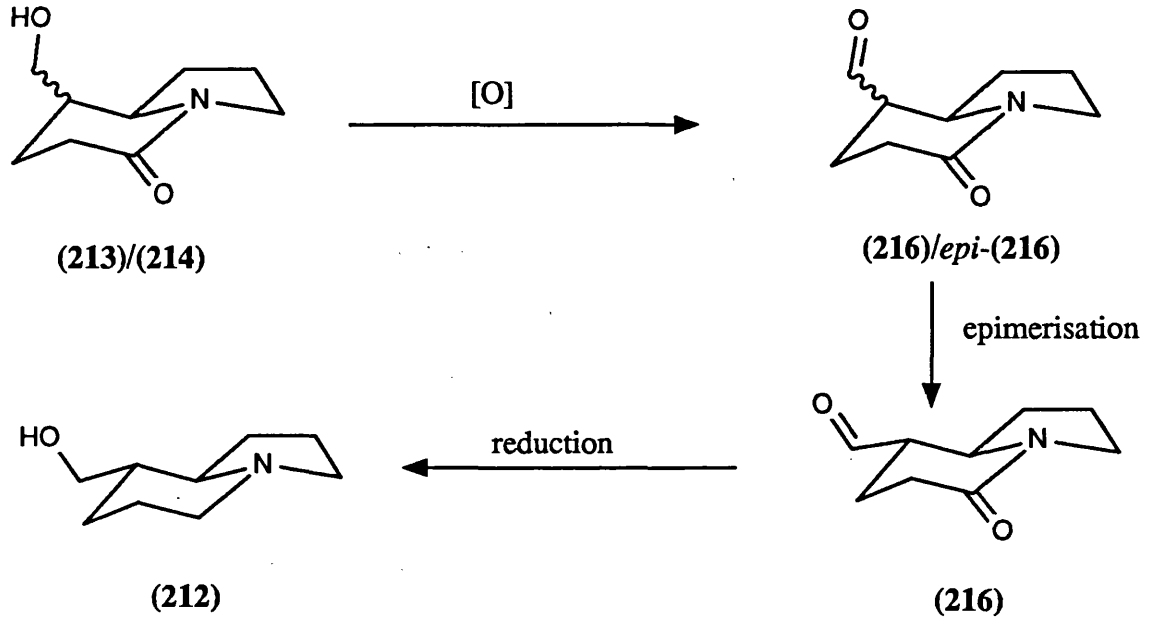


ent-(77) **(213)** **(214)** **(215)** **(212)**

Scheme 188

Conversion of *ent*-**(77)** to tashiromine requires hydration of the exocyclic methylene group, in a regio- and stereoselective manner, and subsequent carbonyl reduction. It was intended that a hydroboration/oxidation sequence would introduce the hydroxyl functionality at the sterically least hindered carbon and that lactam reduction would occur either under hydroboration conditions or on subsequent reduction with lithium aluminium hydride.

Treatment of the lactam *ent*-**(77)** with borane-dimethylsulphide complex (BMS) in THF (Scheme 188) at room temperature effected hydroboration within 30 min. as evidenced by t.l.c.. Oxidative hydrolysis of the resultant alkylborane with aqueous hydrogen peroxide according to the literature procedure[212] resulted in the formation of epimeric alcohols **(213/214)** in a ratio of 1.6:1. The lactam subunit at this stage was apparently still intact, as evidenced by NMR and IR analysis of the reaction mixture. Assignment of stereochemistry was made on the basis of reduction of the epimeric mixture with lithium aluminium hydride to form tashiromine and its C8-epimer **(215)**, which has also been characterised previously. The product mixture comprised two components in a 1.6:1 ratio, with the epimer of tashiromine predominating.



(213)/(214) **(216)/*epi*-(216)** **(216)** **(212)**

Scheme 189

Scrutiny of the structure of tashiromine reveals a *trans* arrangement of substituents at C8 and C8a. It was expected, therefore, that oxidation of the alcohol functionality in the hydroxylactam mixture **(213/214)** followed by epimerisation of the resulting aldehyde would effect conversion to the thermodynamically favoured *trans* isomer (Scheme 189). Reduction would then furnish the required target molecule as the major isomer.

In the event, oxidation of the hydroxylactam mixture **(213/214)** was carried out using pyridine-sulphur trioxide complex in DMSO[129] and complete conversion to 2 new components was indicated by t.l.c.. Addition of 1 equivalent sodium methoxide to a solution of this aldehyde mixture in methanol resulted in the disappearance of the major aldehyde component and only the original minor aldehyde isomer was observed in the reaction mixture. Isolation of this single aldehyde component followed by reduction with lithium aluminium hydride afforded tashiromine in 7% overall yield from the unsaturated lactam *ent*-**(77)** following chromatography. None of the epimeric component was observed in the proton NMR spectrum of the crude reaction mixture, indicating a considerable thermodynamic preference for the desired aldehyde at the epimerisation step.

The material exhibited spectral characteristics identical to those reported previously and a value for the optical rotation was obtained on a small sample (5.4mg); $[\alpha]_D^{20}$ +12.8° (c 0.54, EtOH).[213]

In summary, therefore, this brief investigation into the synthesis of (+)-tashiromine has underlined the versatility of the bicyclic lactam (**77**) and how it may provide access to a variety of indolizidine-based products. The completion of the synthesis indicates the potential of the strategy applied although the poor overall yield suggests a need for refinement of the methods employed.

2.13 Future Work

The work described has introduced a number of new areas for future investigation, both in the area of asymmetric electrophile-mediated cyclisations and in natural product synthesis.

In particular, a study into the scope and mechanism of the silver(I)-mediated process is required in order to allow a clearer understanding of the basis of asymmetric induction during the cyclisation. Efforts are currently focussing on this aspect.

The continued search for a transformation that provides highly functionalised cyclised products with impressive diastereoselectivities is another area demanding attention. A number of alternative approaches are available including *in situ* functionalisation of intermediate vinyl silver species, or refinement of the copper(I)-mediated cyclisation introduced in section 2.6.

In the field of natural product synthesis, the undoubted versatility of the bicyclic lactam (**77**) could be exploited in further synthesis of complex indolizidine natural products. As an example, allylic oxidation of the unsaturated lactam would provide access to the structurally challenging allo-pumiliotoxin alkaloid class.

Alternatively, extension of the synthetic methodology to vinylpiperidines would allow an entry into a wide range of quinolizidine-based natural products.

EXPERIMENTAL

Instrumentation and Experimental Techniques

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and peaks are reported (υ_{max}) in wavenumbers (cm^{-1}) with reference to the polystyrene 1028cm^{-1} peak. The abbreviation "br" is appended to a peak to indicate significant broadening. Spectra of liquid samples were taken as thin films on sodium chloride plates, or as solutions in chloroform ($CHCl_3$). Spectra of solid samples were taken as solutions in chloroform.

Routine mass spectra were obtained in the electron impact mode (E.I.) with an ionising potential of 70eV and in the chemical ionisation mode (C.I.), with *iso*-butane as reagent gas. These along with high resolution accurate mass determinations in the (E.I.) mode were recorded with a VG Analytical 7070E instrument and a VG2000 data system. High resolution accurate mass determinations in the (C.I.) mode were recorded at Shell Research Centre, Sittingbourne, with a Finnegan MAT90 instrument using methane as reagent gas. Where possible, the molecular ion peak is indicated along with all sizeable fragments. Where a molecular ion was not observed, a high resolution accurate mass determination in the E.I. mode was carried out on a fragment ion.

Proton magnetic resonance (proton NMR) spectra were recorded at 60MHz on Hitachi Perkin-Elmer high resolution R-23B and Varian Anaspect EM-360 spectrometers, at 270MHz on a Jeol GNM GX FT 270 spectrometer and at 400MHz on a Jeol GNM GX FT 400 spectrometer. Carbon 13 magnetic resonance (^{13}C NMR) spectra were recorded on a Jeol GNM GX FT 270 spectrometer operating at 68MHz and using 90 and 135 DEPT pulse sequences to aid in multiplicity determination. Proton and ^{13}C NMR spectra are expressed in parts per million (δ) downfield from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) and multiplet (m). The abbreviation "br" is appended

to a multiplicity to indicate significant broadening.

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser. Optical rotations were measured using a Perkin-Elmer 141 polarimeter with concentration (c) expressed in g/100ml.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light (when possible) or using a reagent (typically potassium permanganate) that would give a colour change with the functional groups present, as described in "Dyeing Reagents for Thin Layer and Paper Chromatography", E. Merck, Darmstadt, 1980.

Unless otherwise stated petrol refers to that fraction of petroleum spirit boiling in the range 60-80°C. Solvents used as eluants in chromatography were dried and distilled prior to use except for diethyl ether (ether), which was dried over sodium wire and used without distillation.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 (Merck 9385) (flash) and 60H silica gel (Merck 7736) for reaction component seperations. A pressure gradient was developed using small, commercially available hand bellows (Gallenkamp). In all cases columns were prepared in the least polar solvent of the eluant mixture and chromatography was carried out with the least polar solvent as initial eluant, then eluting with solvent mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the

column. Preparative layer chromatography was performed using Merck 60 F_{254} silica gel, glass supported plates.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was redistilled immediately prior to use.

Glassware used for water sensitive reactions was baked in an oven at 120°C for approximately 12h and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirrer bars were, however, additionally flame dried under a stream of dry nitrogen. In all experiments the excess solvent was removed with a Büchi rotary evaporator using a water aspirator at room temperature to avoid unnecessary decomposition. All yields quoted are of purified products and are uncorrected unless otherwise stated.

All other reagents and solvents were purified and dried, when required, according to accepted procedures.[214]

Pumiliotoxin 251D (**7**) and (+)-Pumiliotoxin 251D hydrochloride (**7**)-HCl.

To a solution of the Z-enelactam Z-(**74**) (16.0mg, 0.06 mmol) in ether (2ml) was added a solution of aluminium hydride in ether (0.18M, 1.8ml, 5.4 eq) at room temperature. After 10 min. the reaction was quenched with saturated aqueous sodium sulphate solution and filtered, washing with dichloromethane. Addition of methanolic HCl to the resulting solution effected conversion to the hydrochloride salt. Evaporation *in vacuo* afforded pumiliotoxin 251D hydrochloride as a colourless solid (11.7mg, 67%). Recrystallisation from ether/petrol yielded colourless crystals. (**7**)-HCl: m.p. 200-201°C (evacuated sealed capillary); $[\alpha]_D^{20}$ +23.6° (c 0.11, MeOH); $[\alpha]_{546}^{20}$ +36.1° (c 0.11, MeOH); δ_H (270 MHz, CD_3OD) (Assignments based on indolizidine numbering system) 5.32 (1H, d, *J* 10 Hz, H-10), 4.36 (1H, d, *J* 13 Hz, H-5β), 3.05-3.59 (4H, m, H-3β, NH, H-5α, H-11), 2.43 and 2.36 (2H, 2 x d, *J* 15 Hz, 2 x H-7), 1.77-2.18 (6H, m, 2 x H-1, 2 x H-2, H-3α, H-8a), 1.12-1.35 (6H, m, 2 x H-12, 2 x H-13, 2 x H-14), 1.28 (3H, s, C8-Me), 1.03 (3H, d, *J* 6.5 Hz, C11-Me), 0.89 (3H, t, *J* 7.5 Hz, $CH_2\underline{CH_3}$); δ_C (68 MHz, CD_3OD) 140.93, 125.75, 74.05, 68.96, 54.33, 52.64, 47.68, 38.60, 33.76, 31.10, 26.30, 24.10, 22.13, 21.76, 20.89, 14.69.

The free base was obtained from the hydrochloride by dilution with saturated aqueous sodium bicarbonate solution, extraction with dichloromethane, drying (Na_2SO_4) and evaporation *in vacuo* at 0°C. (**7**): υ_{max} ($CHCl_3$) 3400, 1660 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.04 (1H, d, *J* 9.5 Hz, H-10), 3.79 (1H, d, *J* 12 Hz, H-5β), 3.04-3.12 (1H, m, H-3β), 2.35 (1H, d, *J* 12 Hz, H-5α), 2.30-2.44 (1H, m, H-11), 2.08-2.30 (1H, m, H-3α), 2.14 (2H, br s, 2 x H-7), 1.94-2.01 (1H, m, H-8a), 1.66-1.78 (4H, m, 2 x H-1, 2 x H-2), 1.11-1.34 (7H, m, 2 x H-12, 2 x H-13, 2 x H-14, OH), 1.13 (3H, s, C8-Me), 0.97 (3H, d, *J* 6.5 Hz, C11-Me), 0.88 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$); δ_C (68 MHz, $CDCl_3$) 134.70 (d), 129.74 (s), 71.68 (d), 68.31 (s), 54.65 (t), 53.16 (t), 48.81 (t), 37.43 (t), 32.05 (d), 29.71 (t), 24.26 (q), 23.22 (t), 22.80 (t), 21.67 (q), 21.05 (t), 14.11 (q). (**7**)-HCl: m/e (E.I.) 251, 166, 112, 70. Exact mass (M^+) 251.2253 (Calcd. for $C_{16}H_{29}NO$ 251.2249).

(R/S)-8-Hydroxy-8-methyl-6(E)-propylidene-(8a R/S)-octahydroindolizidine (**31**).
To a solution of the enelactam E-(**195**) (24.5mg, 0.10 mmol) in ether (3ml) was added a solution of DiBAl in toluene (1.5M, 0.25ml, 3.8 eq) and the reaction stirred at room temperature for 1h. The reaction was quenched with saturated aqueous ammonium chloride solution, filtered and concentrated *in vacuo*. Adequate purification was achieved by dissolving in dilute aqueous hydrochloric acid (5ml), extracting with ethyl acetate (2ml), neutralising the aqueous layer with sodium bicarbonate and extracting with ethyl acetate (2x). Dyring (Na_2SO_4) and evaporation *in vacuo* afforded the title compound as a colourless oil, (18.1mg, 79%). υ_{max} ($CHCl_3$) 3480, 1620 cm^{-1}; δ_H (270 MHz, $CDCl_3$) (Assignments based on indolizidine numbering system) 5.47 (1H, t, *J* 7.5 Hz, H-10), 3.39 (1H, d, *J* 11.5 Hz, H-5β), 3.08-3.14 (1H, m, H-3β), 2.66-2.72 (1H, m, H-8a), 2.64 (1H, d, *J* 12 Hz, H-5α), 1.97-2.28 (4H, m, 2 x H-7, H-3α, OH), 1.70-1.83 (6H, m, 2 x H-1, 2 x H-2, 2 x H-11), 1.26-1.39 (4H, m, 2 x H-12, 2 x H-13), 1.18 (3H, s, CH_3), 0.89 (3H, m, $CH_2\underline{CH_3}$); δ_C (68 MHz, $CDCl_3$) 132.43, 131.04, 72.1, 68.40, 61.89, 54.23, 40.96, 32.01, 27.08, 24.78, 23.19, 22.38, 20.95, 13.98. m/e (E.I.) 223, 166, 70. Exact mass (M^+) 223.1929 (Calcd. for $C_{14}H_{25}NO$ 223.1935).

(R/S)-8-Hydroxy-8-methyl-6(Z)-propylidene-(8a R/S)-octahydroindolizidine (**32**).
To a solution of the enelactam Z-(**195**) (9.6mg, 0.04 mmol) in ether (2ml) was added a solution of aluminium hydride in ether (0.07M, 2ml, 3.5 eq) at room temperature and the reaction stirred for 30 min.. Quenching with saturated aqueous sodium sulphate solution was followed by filtration and concentration *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate, afforded the title compound as a colourless oil (3.8mg, 43%). υ_{max} ($CHCl_3$) 3400, 1620 cm^{-1}; δ_H (270 MHz, $CDCl_3$) (Assignments based on indolizidine numbering system) 5.28 (1H, t, *J* 7.5 Hz, H-10), 3.83 (1H, d, *J* 12 Hz, H-5β), 3.06-3.13 (1H, m, H-3β), 2.36 (1H, d, *J* 12 Hz, H-5α), 2.23-2.33 (1H, m, H-8a), 2.15 (1H, d, *J* 9 Hz, H-3α),

1.95-2.14 (2H, m, 2 x H-7), 1.68-1.80 (7H, 2 x H-1, 2 x H-2, 2 x H-11, OH), 1.30-1.36 (4H, m, 2 x H-12, 2 x H-13), 1.14 (3H, s, C8-CH_3), 0.89 (3H, t, *J* 7 Hz, C11-CH_3); δ_C (68 MHz, $CDCl_3$) 130.68, 128.12, 71.71, 68.37, 54.49, 52.71, 48.78, 31.98, 27.18, 24.32, 23.19, 22.28, 21.05, 13.95. m/e (E.I.) 223, 166, 70. Exact mass (M^+) 223.1932 (Calcd. for $C_{14}H_{25}NO$ 223.1935).

(S)-8-Hydroxy-8-methyl-6(Z)-[(R)-2-methylhexylidene]-(8a S)-octahydro-5-indolizidinone Z-(**74**).

To a solution of the aldol (**209c**) (22.2mg, 0.078 mmol) in toluene (2ml) was added DCC in toluene (0.36M, 0.25ml, 1.2 eq) and copper(I) chloride (9.0mg, 1.9 eq) and the reaction heated to reflux for 24h. Addition of dilute aqueous ammonia (5ml) was followed by extraction with ethyl acetate (3x10ml), drying ($MgSO_4$) and concentration *in vacuo*. Silica gel chromatography, eluting with ethyl acetate/petrol (1:4), afforded the title compound as a colourless solid (20.4mg, 98%). Recrystallisation from ether/petrol afforded colourless crystals. m.p. 135-138°C; $[\alpha]_D^{21}$ -28.0° (c 0.40, $CHCl_3$); υ_{max} ($CHCl_3$) 3400, 1650, 1600 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.64 (1H, dd, *J* 9.5, 2 Hz, HC=), 3.79-3.84 (1H, m, MeCH), 3.56 (2H, dd, *J* 9.5, 5 Hz, NCH_2), 3.46 (1H, dd, *J* 10.5, 6 Hz, NCH), 2.70 (1H, dd, *J* 15, 2 Hz, HC-C=), 2.44 (1H, d, *J* 15 Hz, HC-C=), 1.75-2.03 (5H, m, 2 x ring CH_2, OH), 1.19-1.34 (6H, m, 3 x CH_2), 1.27 (3H, s, CH_3), 0.97 (3H, d, *J* 6.5 Hz, $CHCH_3$), 0.86 (3H, t, *J* 7 Hz, CH_2CH_3); δ_C (68 MHz, $CDCl_3$) 163.80 (s), 152.28 (d), 122.86 (s), 67.69 (s), 66.52 (d), 47.03 (t), 45.54 (t), 37.17 (t), 32.43 (d), 29.58 (t), 26.08 (t), 25.17 (q), 22.87 (t), 22.15 (t), 20.73 (q), 14.04 (q). m/e (E.I.) 265, 222, 149, 120, 91. Exact mass (M^+) 265.2047 (Calcd. for $C_{16}H_{27}NO_2$ 265.2039).

(S)-8-Hydroxy-8-methyl-6(E)-[(R)-2-methylhexylidene]-(8a S)-octahydro-5-indolizidinone E-(**74**).

To a solution of the aldol mixture (**209a,b**) (12.6mg, 0.045 mmol) in pyridine (2ml) was added methanesulphonyl chloride (10µl, 3.0 eq) at 0°C, the reaction

warmed to room temperature and stirred for 15 min.. Dilution with dilute aqueous hydrochloric acid (5ml), extraction with ethyl acetate (3x10ml) followed by drying (Na_2SO_4) and evaporation *in vacuo* afforded on silica gel chromatography, eluting with ethyl acetate/petrol (1:3), the mesylate mixture (11.8mg) as a colourless oil. This was dissolved in methanol (3ml), powdered potassium hydroxide (25.0mg, 9.9 eq) added and the reaction mixture gradually warmed to reflux over 45 min.. After 2h at reflux, the reaction mixture was cooled, diluted with water (5ml), extracted with ethyl acetate (3x10ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate/petrol (1:3), afforded Z-(**74**) (2.1mg) and the title compound as a colourless solid (6.5mg) in a combined yield of 73%. Further purification by recrystallisation from dichloromethane/petrol yielded colourless crystals. m.p. 175-176°C; $[\alpha]_D^{17}$ -43.3° (c 0.33, $CHCl_3$); υ_{max} ($CHCl_3$) 3400, 1660, 1600 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.81 (1H, dd, *J* 10, 2 Hz, HC=), 3.55-3.66 (2H, m, NCH_2), 3.50 (1H, dd, *J* 9, 4 Hz, NCH), 2.76 (1H, d, *J* 16 Hz, HC-C=), 2.40 (1H, dd, *J* 16, 2 Hz, HC-C=), 2.36-2.44 (1H, m, MeCH), 1.76-2.04 (4H, m, 2 x ring CH_2), 1.21-1.43 (7H, m, 3 x CH_2, OH), 1.31 (3H, s, CH_3), 0.97 (3H, d, *J* 6.5 Hz, $CHC\underline{H}_3$), 0.87 (3H, t, *J* 7 Hz, $CH_2C\underline{H}_3$); δ_C (68 MHz, $CDCl_3$) 163.77 (s), 147.71 (d), 124.16 (s), 67.82 (s), 65.81 (d), 46.25 (t), 39.53 (t), 36.56 (t), 32.79 (d), 29.68 (t), 26.40 (t), 25.27 (q), 22.80 (t), 22.22 (t), 19.79 (q), 13.98 (q). m/e (E.I.) 265, 222. Exact mass (M^+) 265.2039 (Calcd. for $C_{16}H_{27}NO_2$ 265.2039).

(S)-8-Hydroxy-8-methyl-(8a S)-octahydro-5-indolizidinone (**75a**).

To a suspension of mercuric acetate (194.8mg, 0.61 mmol) in THF/water (1:1, 4ml) was added a solution of lactam (**77**) (71.0mg, 0.47 mmol) in THF (2ml) at room temperature. The reaction was stirred for 3h, followed by addition of aqueous sodium hydroxide (2M, 1ml) and then a solution of sodium borohydride (10mg, 0.26 mmol) in aqueous sodium hydroxide (2M, 1ml). The reaction mixture immediately turned dark grey, was stirred for five minutes and then filtered

through Celite, washing with dichloromethane. Separation of the organic layer, saturation of the aqueous layer with sodium chloride and further extraction with dichloromethane (2x30ml) afforded, on drying (Na_2SO_4) and evaporation of the combined organic layers, a light grey residue. This was diluted with ethyl acetate and once again filtered through a plug of Celite to afford, on evaporation, **(75a,b)** as a colourless glass, (10:1 mixture, 75.8 mg, 95%) which could be used without further purification. A sample of diastereomerically pure **(75a)** was obtained by recrystallisation from petrol/ether. m.p. 90-92°C; $[\alpha]_D^{21}$ -47.0° (c 0.97, $CHCl_3$); υ_{max} ($CHCl_3$) 3380, 1620 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 3.55 (2H, dd, *J* 11, 5 Hz, NCH_2), 3.37 (1H, dd, *J* 10, 5.5 Hz, NCH), 2.71 (1H, s, OH), 2.56 (1H, ddd, *J* 19.5, 10.5, 7.5 Hz, COCH), 2.40 (1H, dd, *J* 19.5, 7.5 Hz, COCH), 1.68-2.03 (6H, m, 3 x CH_2), 1.31 (3H, s, CH_3); δ_C (68 MHz, $CDCl_3$) 169.18 (s), 67.08 (s), 66.20 (d), 45.64 (t), 34.87 (t), 27.99 (t), 26.30 (q), 26.08 (t), 21.83 (t). m/e (E.I.) 169, 111, 83, 70. Found: C, 63.9; H, 8.9; N, 8.3%. (Calcd. for $C_9H_{15}NO_2$; C, 63.6; H, 9.1; N, 7.9%).

(R)-2-Methylhexanal **(76)**.

To a solution of the alcohol **(207)** (58.2mg, 0.50 mmol) in DMSO (2ml) was added triethylamine (0.43ml, 6.9 eq) followed by a DMSO solution of pyridine-sulphur trioxide complex (240mg, 3.4 eq in 2ml) and the reaction stirred at room temperature for 30 min.. Dilution with water (5ml), extraction with ether/30-40° petrol (1:1, 3x10ml), washing the combined organic layers with water (3x10ml), dilute aqueous hydrochloric acid (3x10ml), drying (Na_2SO_4) and evaporation *in vacuo* at 0°C afforded the title compound which was used without further purification.

8-Methylene-(8a S)-octahydro-5-indolizidinone **(77)** and 8-Methylene-(8a R)-octahydro-5-indolizidinone *ent*-**(77)**.

To a solution of the ethyl ester **(170)** (1.29 g, 4.3 mmol) in methanol (60ml) was

added powdered sodium hydroxide (2.41g, 14 eq) and the reaction heated to reflux for 30 min. after which time it was cooled, concentrated *in vacuo* and the last traces of solvent removed under high vacuum. Acetic anhydride (50ml) was added cautiously to the resulting solid and once the addition was complete, the reaction was heated to reflux for 2h. Cooling was followed by dilution with dichloromethane (100ml) and washing with aqueous sodium hydroxide (2M, 20ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford a residue which was chromatographed on silica gel, eluting with ethyl acetate, to yield the title compound as a colourless oil (491mg, 76%).

(77): b.p. (bulb to bulb) 165°C (0.1 mm Hg); $[\alpha]_D^{20}$ -98.3 (c 1.2, $CHCl_3$); υ_{max} (film) 1620 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.98 and 4.92 (2H, 2 x s, HC=), 3.97-4.04 (1H, m, HC-C=), 3.44-3.69 (2H, m, NCH_2), 2.38-2.51 and 2.16-2.25 (4H, 2 x m, $COCH_2$, H_2C-C=), 1.97-2.08 (1H, m, $\underline{H}CH_2$), 1.63-1.94 (3H, m, HCH_2); δ_C (68 MHz, $CDCl_3$) 169.38 (s), 143.46 (s), 109.15 (t), 60.85 (d), 44.66 (t), 32.57 (t), 30.94 (t), 29.45 (t), 22.25 (t);

ent-**(77)**: $[\alpha]_D^{19}$ +60.8° (c 1.2, $CHCl_3$).

(77)/*ent*-**(77)**: m/e (E.I.) 151, 136. Exact mass (M^+) 151.0983 (Calcd. for $C_9H_{13}NO$ 151.0996).

General procedure (A) for formation of cyclisation substrates *via* reductive amination of 4,5-hexadienal

To a 0.5M solution of 4,5-hexadienitrile in dry ether was added 25% solution of DiBAl in toluene (1 equivalent) at room temperature. The reaction was allowed to proceed for 1h, cooled to 0°C and quenched with aqueous hydrochloric acid (2M), the resultant biphasic mixture being stirred for 10 min.. The organic layer was separated, the aqueous phase extracted with ether (2x) and the combined organic extracts dried ($MgSO_4$). The appropriate primary amine (1 eq) was added to this

suspension and allowed to stir overnight. Filtration and concentration *in vacuo* afforded the crude imine which was then dissolved in absolute ethanol or dry methanol. Sodium borohydride (0.5 eq) was added to the solution at room temperature and the reaction stirred for 30 min.. Dilution with water, extraction with ether (3x), drying ($MgSO_4$) and concentration *in vacuo* was followed by chromatography on silica gel to afford the allenic amine as a colourless oil.

(R)-*N*-(α-Methylbenzyl)hexa-4,5-dienylamine R-(**88**) and
(S)-*N*-(α-Methylbenzyl)hexa-4,5-dienylamine S-(**88**).

R-(**88**): Obtained in 71% yield. b.p.(bulb to bulb) 155°C (1.4mmHg); $[\alpha]_D^{25}$ +52.7° (c 0.15, Et_2O); υ_{max} (film) 3300, 1950, 1600 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.21-7.31 (5H, m, ArH), 5.05 (1H, p, *J* 7 Hz, HC=), 4.62 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.74 (1H, q, *J* 7 Hz, NCH), 2.40-2.60 (2H, m, NCH_2), 1.90-2.07 (2H, m, H_2C-C=), 1.54-1.65 (3H, m, CH_2, NH), 1.34 (3H, d, *J* 7 Hz, CH_3); δ_C (68MHz, $CDCl_3$) 208.46 (s), 145.80 (s), 128.38 (d), 126.82 (d), 126.53 (d), 89.65 (d), 74.89 (t), 58.35 (d), 47.10 (t), 29.55 (t), 25.98 (t), 24.39 (q). *m/e* (E.I.) 201, 186, 105. Exact mass (M^+) 201.1508 (Calcd. for $C_{14}H_{19}N$ 201.1517).

S-(**88**): $[\alpha]_D^{25}$ -46.9°, (c 1.28, Et_2O).

(R)-Methyl 2-(*N*-hexa-4,5-dienylamino)-2-phenylacetate (**89**).

Obtained in 32% yield. $[\alpha]_D^{25}$ -82.4° (c 0.46, Et_2O); υ_{max} (film) 3300, 1960, 1740 cm^{-1}; δ_H (270 MHz, $CDCl_3$). 7.30-7.38 (5H, m, ArH), 5.08 (1H, p, *J* 7 Hz, HC=), 4.65 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 4.37 (1H, s, PhCH), 3.69 (3H, s, OCH_3), 2.52-2.63 (2H, m, NCH_2), 2.04 (qt, *J* 7, 3.5 Hz, H_2C-C=), 2.00-2.15 (1H, br s, NH), 1.64 (2H, p, *J* 7 Hz, CH_2). m/e (C.I.) 246, 186 (E.I.) 186. Exact mass (M^+ -CO_2Me) 186.1271 (Calcd. for $C_{13}H_{16}N$ 186.1282).

(R)-*N*-Methyl-2-(*N*-hexa-4,5-dienylamino)-2-phenylacetacemide (**90**).

Obtained in 27% yield. $[\alpha]_D^{25}$ -43.7° (c 2.3, Et_2O); υ_{max} (film) 3320, 1955, 1655

cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.25-7.40 (5H, m, ArH), 7.20 (1H, br s, CONH), 5.09 (1H, p, *J* 7 Hz, HC=), 4.66 (2H, dt, *J* 7 Hz, 3.5Hz, H_2C=), 4.14 (1H, s, PhCH), 2.83 and 2.81 (3H, 2 x s, NCH_3), 2.61-2.67 (2H, m, NCH_2), 2.06 (2H, qt, *J* 7, 3.5 Hz, H_2C-C=), 1.75 (1H, br s, NH), 1.63 (2H, p, *J* 7 Hz, CH_2); δ_C (68 MHz, $CDCl_3$) 208.36 (s), 172.65 (s), 139.31 (s), 128.67 (d), 127.92 (d), 127.18 (d), 89.26 (d), 75.02 (t), 67.63 (d), 47.87 (t), 29.03 (t), 25.88 (q), 25.62 (t). m/e (C.I.) 245, 186 (E.I.) 186. Exact mass (M^+ -CONHMe) 186.1286 (Calcd. for $C_{13}H_{16}N$ 186.1282).

(S)-Methyl 2-(*N*-hexa-4,5-dienylamino)-3-phenylpropionate **(91).**

Obtained in 27% yield. $[\alpha]_D^{25}$ +9.2° (c 0.76, Et_2O); υ_{max} (film) 3300, 1950, 1730 ,1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.17-7.32 (5H, m, ArH), 5.06 (1H, p, *J* 7 Hz, HC=), 4.64 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.64 (3H, s, OCH_3), 3.54 (1H, t, *J* 7 Hz, NCH), 2.98 (2H, d, *J* 7 Hz, $PhCH_2$), 2.47-2.69 (2H, m, NCH_2), 1.97 (2H, qt, *J* 7, 3.5 Hz, H_2C-C=), 1.8-1.9 (1H, br s, NH), 1.58 (2H, p, *J* 7.5 Hz, CH_2). m/e (E.I.) 259, 200, 168. Exact mass (M^+ -CO_2Me) 200.1434 (Calcd. for $C_{14}H_{18}N$ 200.1438).

(S)-*N*-[1-(methoxymethyl)-2-phenylethyl]hexa-4,5-dienylamine **(92).**

Obtained in 28% yield. $[\alpha]_D^{25}$ +6.25° (c 0.4 EtOH); υ_{max} (film) 1600, 1950, 3300 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.17-7.32 (5H, m, ArH), 5.07 (1H, p, *J* 7 Hz, HC=), 4.65 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.32 (3H, s, OCH_3), 3.21-3.33 (2H, m, NCH_2), 2.90-2.99 (1H, m, NCH), 2.66-2.84 (4H, m, OCH_2, $PhCH_2$), 2.00 (2H, qt, *J* 7, 3.5 Hz, H_2C-C=), 1.70-1.80 (1H, br s, NH), 1.58 (2H, p, *J* 7.5 Hz, CH_2). m/e (C.I.), 246, 154 (E.I.) 200, 154. Exact mass (M^+ -CH_2OMe) 200.1432 (Calcd. for $C_{14}H_{18}N$ 200.1438).

Methyl (S)-2-(*N*-hexa-4,5-dienylamino)-3-methylbutanoate **(93).**

Obtained in 43% yield. $[\alpha]_D^{25}$ -16.1° (c0.82, Et_2O); υ_{max} (film) 3310, 1945, 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.10 (1H, p, *J* 7 Hz, HC=), 4.66 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.72 (3H, s, OCH_3), 2.58-2.65 and 2.39-2.49 (2H, 2 x m, CH_2N), 2.06 (2H,

qt, *J* 7, 3.5 Hz), H_2C-C=), 1.89 (1H, octet, *J* 7 Hz, Me_2CH), 1.45-1.68 (3H, m, CH_2, NH), 0.95 (3H, d, *J* 7 Hz, CH_3), 0.93 (3H, d, *J* 7 Hz, CH_3). m/e (C.I.) 212, 152 (E.I.) 168, 152. Exact mass (M^+ -Me_2CH) 152.1431 (Calcd. for $C_{10}H_{18}N$ 152.1438).

(R)-2-(*N*-Hexa-4,5-dienylamino)-2-phenylethanol (96).

To a solution of lithium aluminium hydride (66mg, 1.74 mmol) in dry ether (5ml) was added a solution of the ester (**89**) (332mg, 1.36 mmol) in ether (4ml) at -78°C. The mixture was allowed to warm to room temperature over 1h, quenched with saturated aqueous sodium sulphate solution, and filtered through Celite, washing the residue with dichloromethane. Concentration *in vacuo* afforded the title compound as a light yellow oil (255mg, 87%). $[\alpha]_D^{25}$ -101.1° (c 0.47, Et_2O); υ_{max} (film) 3350 (br), 1950, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.24-7.39 (5H, m, ArH), 5.07 (1H, p, *J* 7 Hz, HC=), 4.63 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.68-3.78 (2H, m, OCH_2), 3.53 (1H, dd, *J* 11, 8 Hz, PhCH), 2.46-2.63 (2H, m, NCH_2), 2.20-2.40 (2H, br, OH, NH), 2.03 (2H, qt, *J* 7, 3.5 Hz, H_2C-C=), 1.55-1.68 (2H, m, CH_2). m/e (C.I.) 218, 186 (E.I.) 186. Exact mass (M^+ -CO_2Me) 186.1292 (Calcd. for $C_{13}H_{16}N$ 186.1282).

(S)-2-(*N*-Hexa-4,5-dienylamino)-3-phenylpropanol (97).

To a solution of lithium aluminium hydride (27mg, 0.7mmol) in dry ether (3ml) was added a solution of the allenic ester (**91**) (190mg, 0.7mmol) in ether (1ml) at -78°C. The reaction was allowed to warm to room temperature over 1h. Addition of saturated aqueous sodium sulphate solution until the aluminium salts precipitated, followed by filtration through Celite and washing with dichloromethane afforded, on concentration *in vacuo*, a yellow solid. Purification by sublimation under high vacuum afforded the title compound as a colourless solid (61mg, 36%). m.p. 64-65°C; $[\alpha]_D^{25}$ +1.7° (c 0.72, Et_2O); υ_{max} ($CHCl_3$) 3400 (br), 1955, 1600 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.16-7.33 (5H, m, ArH), 5.06 (1H, p,

J 7 Hz, HC=), 4.65 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.60 (1H, dd, *J* 11, 4 Hz, C<u>H</u>OH), 3.30 (1H, dd, *J* 11, 5 Hz, C<u>H</u>OH), 2.80-2.93 (1H, m, NCH), 2.56-2.77 (4H, m, NCH_2, $PhCH_2$), 2.00 (2H, qt, *J* 7, 3.5 Hz and 2H, br, H_2C-C=, NH, OH), 1.57 (2H, p, *J* 7 Hz, CH_2). m/e (C.I.) 232, 140. Found C, 78.2; H, 9.3, N, 6.0%. (Calcd. for $C_{15}H_{21}NO$; C, 77.9, H, 9.1; N, 6.1%).

<u>(R)-*N*-Hexa-4,5-dienyl-*N'*-methyl-1-phenyldimethylene diamine **(100)**.</u>

To a solution of the allenic amide **(90)** (348mg, 1.4 mmol) in dry ether (10ml) was added a 25% solution of DiBAL in toluene (3.8ml, 4 eq) and the reaction stirred at room temperature for 14h. Quenching with saturated aqueous sodium sulphate solution followed by extraction with dichloromethane (3x10ml) afforded, on drying (Na_2SO_4) and concentraton *in vacuo* a residue which was chromatographed on silica gel, eluting with ethyl acetate/methanol (5:1) to afford the product as a light yellow oil (197mg, 95% based on recovered **(89)**, 120mg). $[\alpha]_D^{25}$ -70.0° (c 0.18, Et_2O); υ_{max} (film) 3310, 1955 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.27-7.35 (5H, m, ArH), 5.05 (1H, p, *J* 7 Hz, HC=), 4.61 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.81 (1H, dd, *J* 8, 6 Hz, PhCH), 3.00-3.20 (2H, br, 2xNH), 2.82 (1H, d, *J* 6 Hz, HCNMe), 2.83 (1H, d, *J* 8 Hz, HCNMe), 2.49-2.54 (2H, m, NCH_2), 2.49 (3H, s, NCH_3), 1.88-2.08 (2H, m, H_2C-C=), 1.60 (2H, p, *J* 7 Hz, CH_2). m/e (C.I.) 231, 186, 134 (E.I.) 186. Exact mass (M^+ -CH_2NHMe) 186.1287 (Calcd. for $C_{13}H_{16}N$ 186.1282).

<u>(R/S)-Allyl 2-(*N*-hexa-4,5-dienylamino)-2-phenylacetate **(102)**.</u>

To a solution of the allenic ester **(89)** (1.39g, 5.67mmol) in allyl alcohol (15ml) was added *p*-toluenesulphonic acid monohydrate (500mg) and the reaction was heated to reflux over 4Å molecular sieves. After 30h, the allyl alcohol was removed by distillation, the residue diluted with dichloromethane (20ml), washed with saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on flash silica eluting with ethyl acetate/petrol (1:3) afforded the title compound as a light yellow oil (561mg, 52%

based on recovered (**89**), 418mg). υ_{max} ($CHCl_3$) 3300, 1955, 1725, 1650 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.29-7.40 (5H, m, ArH), 5.76-5.92 (1H, m, HC=), 5.06-5.21 (3H, m, HC==, H_2C=), 4.58-4.67 (4H, m, H_2C==, OCH_2), 4.39 (1H, s, NCH), 2.52-2.66 (2H, m, NCH_2), 2.14 (1H, br, NH), 2.04 (2H, qt, *J* 7, 3.5 Hz, H_2C-C==), 1.64 (2H, p, *J* 7 Hz, CH_2). δ_C (68MHz, $CDCl_3$) 208.49 (s), 172.72 (s), 138.24 (s), 131.78 (d), 128.64 (d), 128.02 (d), 127.41 (d), 118.19 (t), 89.52 (d), 74.96 (t), 65.58 (d), 65.49 (t), 47.06 (t), 29.32 (t), 25.82 (t). m/e (E.I.) 271, 230, 186 (C.I.) 272, 186. Exact mass (MH^+) 272.167 (Calcd. for $C_{17}H_{22}NO_2$ 272.165).

General procedure (B) for silver(I)-mediated cyclisation.

To a 0.5M solution of the appropriate allenic amine in dry dichloromethane was added silver triflate or silver tetrafluoroborate (see Tables in text for molar proportion), the reaction mixture flushed with nitrogen, sealed and stirred under light-free conditions at room temperature until completion of reaction as indicated by t.l.c.(typically 2-3h). Water and dichloromethane were then added, the organic layer separated and combined with two further extracts. Following drying (Na_2SO_4) and concentration *in vacuo*, the reaction mixture was analysed by proton NMR. Where necessary or appropriate, the product was further purified or the diastereoisomers separated by silica gel chromatography (see Tables in text for isolated product yields).

N-[(R)-α-Methylbenzyl]-(R/S)-2-vinylpyrrolidine (**103a,b**).

υ_{max} (film) 1640,1600, 1500 cm^{-1}; δ_H (270MHz, $CDCl_3$) (**103a**): 7.23-7.31 (5H, m, ArH), 5.83 (1H, ddd, *J* 17.5, 10, 8.5 Hz, HC=), 5.13 (1H, dd, *J* 17.5, 2 Hz, *cis*-HC=), 5.12 (1H, dd, *J* 10, 2 Hz, *trans*-HC=), 3.87 (1H, q, *J* 7 Hz, PhCH), 2.85-2.94 (2H, m, HC-C=, NCH), 2.32 (1H, q, *J* 8.5 Hz, NCH), 1.58-1.82 (4H, m, 2xCH_2), 1.44 (3H, d, *J* 7 Hz, CH_3); (**103b**): 7.23-7.31 (5H, m, ArH), 5.71 (1H, ddd,

J 17.5, 10, 8.5 Hz, HC=), 5.00 (1H, dd, *J* 17.5, 2 Hz, *cis*-HC=), 4.93 (1H, dd, *J* 10, 2 Hz, *trans*-HC=), 3.80 (1H, q, *J* 7 Hz, PhCH), 3.26 (1H, q, *J* 7 Hz, NCH), 2.65-2.75 (1H, m, HC-C=), 2.48 (1H, q, *J* 8 Hz, NCH), 1.58-2.00 (4H, m, $2xCH_2$), 1.34 (3H, d, *J* 7 Hz, CH_3). **(103a,b)**: m/e (E.I.) 201, 186. Exact mass (M^+) 201.1526 (Calcd. for $C_{14}H_{19}N$ 201.1517).

Methyl (R)-phenyl[(S)-2-vinylpyrrolidin-1-yl]acetate **(104a).**

$[\alpha]_D^{25}$ -85.5° (c 0.22, Et_2O); υ_{max} ($CHCl_3$) 1735, 1630 cm^{-1}; δ_H (270MHz, $CDCl_3$) (Corresponding shifts of selected signals for minor isomer **(104b)** indicated in italics) 7.29-7.40 (5H, m, ArH), 5.79 (1H, ddd, *J* 18, 10, 9 Hz, HC=), 5.13 (1H, dd, *J* 18, 2 Hz, *cis*-HC=), 5.09 (1H, dd, *J* 10, 2 Hz, *trans*-HC=), 4.29 *(4.56)* (1H, s, PhCH), 3.62 *(3.70)* (3H, s, OCH_3), 2.86-3.05 (2H, m, HC-C=, NCH), 2.20 (1H, q, *J* 8 Hz, NCH), 1.58-1.95 (4H, m, $2xCH_2$). m/e (C.I.) 246, 186 (E.I.) 186. Exact mass (M^+ -CO_2Me) 186. 1284 (Calcd. for $C_{13}H_{16}N$ 186.1282).

N-Methyl-(R)-phenyl[(S)-2-vinylpyrrolidin-1-yl]acetamide **(105a,).**

Procedure (i): General procedure (B).

Procedure (ii):

To a solution of the ester **(104a)** (29.2mg, 0.12 mmol) in methanol (1ml) was added 30% aqueous solution of methylamine (2ml) and the reaction stirred at room temperature overnight. Addition of water (2ml) and extraction with dichloromethane (2x10ml), drying of combined organic layers (Na_2SO_4), concentration *in vacuo* and chromatography on silica gel, eluting with petrol/ethyl acetate (1:1) afforded **(105a)** as a colourless oil (13.8mg, 47%).

Procedure (iii):

To a solution of the vinyl iodide **(180a,b)** (26.0mg, 0.07mmol) (11:1 mixture of diastereoisomers) in benzene (3ml) was added tri-*n*-butyltin hydride (50µl, 2eq) and the reaction heated at reflux for 3h. The reaction mixture was concentrated *in vacuo*, diluted in dichloromethane, washed with water (2ml), the organic layer

dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel, eluting with petrol/ethyl acetate (3:1) afforded **(105a)** as a colourless oil, (4.7mg, 27%). υ_{max} ($CHCl_3$) 3360, 1655 cm^{-1}; δ_H (270MHz, $CDCl_3$) (Corresponding shift of selected signals for minor isomer **(105b)** indicated in italics) 7.16-7.45 (6H, m, ArH, NH), 5.71 *(5.63)*, (1H, ddd, *J* 18, 10, 8.5Hz, HC=), 5.23 (1H, dd, *J* 18, 2Hz, *cis*-HC=), 5.19 (1H, dd, *J* 10, 2Hz, *trans*-HC=), 4.39 *(4.15)* (1H, s, PhCH), 2.94-3.05, 2.73-2.83 (2H, 2xm, NCH, HC-C=), 2.86, 2.84 *(2.81, 2.83)* (3H, 2xs, NCH_3), 2.00-2.15 (1H, m, NCH), 1.52-1.94 (4H, m, 2xCH_2). m/e (C.I.) 245, 186 (E.I.) 186. Exact mass (M^+-CONHMe) 186.1269 (Calcd. for $C_{13}H_{16}N$ 186.1282).

N-[(R)-α-(Hydroxymethyl)benzyl]-(S)-2-vinylpyrrolidine **(106a)**.

Procedure (i): General procedure (B).

Procedure (ii):

To a solution of the methyl ester **(104a)** (45.0mg, 0.18mmol) in ether (2ml) was added lithium aluminium hydride (13.0mg, 0.35mmol) at -78°C. The reaction was allowed to warm to room temperature over 1h, quenched with saturated aqueous sodium sulphate solution and filtered through Celite, washing the residue with dichloromethane. Concentration *in vacuo* afforded the alcohol **(106a)** (35.6mg, 89%).

$[\alpha]_D^{25}$ -149° (c 0.49, $CHCl_3$); υ_{max} ($CHCl_3$)(Corresponding shift of selected signals for minor isomer **(106b)** indicated in italics) 3400 (br), 1630, 1600, 1580 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.14-7.40 (5H, m, ArH), 5.73 (1H, ddd, *J* 18, 10, 8.5 Hz, HC=), 5.27 *(5.06)* (1H, dd, *J* 10, 2 Hz, *cis*-HC=), 5.24 *(4.99)* (1H, dd, *J* 10, 2 Hz, *trans*-HC=), 3.92-4.07 (2H, m, OCH_2), 3.62 (1H, dd, *J* 9, 4 Hz, NCH), 2.50-3.30 (1H, br s, OH), 2.91-3.04 (2H, m, NCH, HC-C=), 2.18 (1H, q, *J* 8 Hz, PhCH), 1.48-1.67 and 1.70-1.87 (4H, 2xm, 2xCH_2). m/e (C.I.) 218, 186. (E.I.) 186. Exact mass (M^+ -CH_2OH) 186.1287 (Calcd. for $C_{13}H_{16}N$ 186.1282).

N-[(R)-α-*N*-Methyl(aminomethyl)benzyl]-(S)-2-vinylpyrrolidine **(107a)**.

Procedure (i): General procedure (B).

Procedure (ii):

To a solution of the amide **(105a,b)** (19.0mg, 0.08 mmol) (9:1 mixture of diastereoisomers) in ether (1ml) was added 25% solution of DiBAl in toluene (0.2ml, 4eq) at room temperature. The reaction was continued for 2h, quenched with saturated aqueous sodium sulphate solution, filtered through celite and the residue washed with dichloromethane. Concentration *in vacuo* afforded the title compound as a colourless oil (14.0mg, 78%) (9:1 mixture of diastereoisomers). υ_{max} ($CHCl_3$) 3300, 1660, 1580 cm^{-1}; δ_H (270MHz, $CDCl_3$) (Corresponding shifts of selected signals for minor isomer **(107b)** indicated in italics) 7.16-7.39 (5H, m, ArH), 5.76 (1H, ddd, *J* 18, 10, 8.5 Hz, HC=), 5.25 *(5.04)* (1H, dd, *J* 18, 2 Hz, *cis*-HC=), 5.23 *(4.96)* (1H, dd, *J* 10, 2 Hz, *trans*-HC=), 4.10 (1H, dd, *J* 10, 5 Hz, PhCH), 3.27-3.42 (3H, m, H_2CNMe, NH), 2.83-2.97 (2H, m, NCH, HC-C=), 2.58 *(2.50)* (3H, s, NCH_3), 2.19 (1H, q, *J* 8 Hz, NCH), 1.48-1.87 (4H, m, 2xCH_2). m/e (C.I.) 231, 186 (E.I.) 186. Exact mass (M^+ -CH_2NHMe) 186.1281 (Calcd. for $C_{13}H_{16}N$ 186.1282).

Allyl (R/S)-phenyl[(S/R)-2-vinylpyrrolidin-1-yl]acetate **(108a)** and Allyl (R/S)-phenyl[(R/S)-2-vinylpyrrolidin-1-yl]acetate **(108b).**

(108a): υ_{max} ($CHCl_3$) 1735, 1645 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.29-7.40 (5H, m, ArH), 5.73-5.93 (2H, m, 2 x HC=), 5.03-5.22 (4H, m, 2 x H_2C=), 4.45-4.66 (2H, m, OCH_2), 4.33 (1H, s, PhCH), 2.91-3.04 (2H, m, HC-C=, NCH), 2.19-2.26 (1H, m, NCH), 1.57-1.96 (4H, m, 2 x CH_2); δ_C (68 MHz, $CDCl_3$) 140.18 (d), 131.95 (d), 129.29 (d), 128.64 (s), 128.22 (d), 128.05 (d), 118.16 (t), 116.41 (t), 69.15 (d), 66.69 (d), 65.19 (t), 50.08 (t), 31.33 (t), 21.86 (t) **(108b):** υ_{max} ($CHCl_3$) 1735, 1645 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.30-7.37 (5H, m, ArH), 5.64-5.95 (2H, m, 2 x HC=), 5.03-5.28 (4H, m, 2 x H_2C=), 4.54-4.71 (3H, m, OCH_2, PhCH), 3.32-3.48 (1H, m, HC-C=), 2.88-3.04 (1H, m, NCH), 2.62-2.78 (1H, m, NCH), 1.50-1.96 (1H, m, $\underline{H}CH_2$), 1.88-2.12 (3H, m, HCH_2). **(108a,b):** m/e (C.I.) 272, 186. Exact mass

(MH^+) 272.167 (Calcd. for $C_{17}H_{22}NO_2$ 272.165).

N-[(S)-1-(methoxymethyl)-2-phenylethyl]-(R/S)-2-vinylpyrrolidine **(109a,b).**

υ_{max} ($CHCl_3$) 1650 cm^{-1}; δ_H (270MHz, $CDCl_3$) **Mixture of diastereoisomers:** 7.14-7.32 (5H, m, ArH), 5.64-5.87 (1H, m, HC=), 5.03-5.25 (2H, m, H_2C=), 2.58-347 (8H, m, NCH_2, OCH_2, $PhCH_2$, 2xNCH), 3.33 and 3.26 (3H, 2 x s, OCH_3), 1.58-2.03 (4H, m, 2xCH_2). m/e (C.I.) 246, 200, 154. Exact mass (MH^+) 246.186 (Calcd. for $C_{16}H_{24}NO$ 246.186).

Methyl 3-phenyl-(S)-2-[(R/S)]-2-vinylpyrrolidin-1-yl]propionate **(110a,b)**

υ_{max} ($CHCl_3$) 1720, 1640, 1600 cm^{-1}. δ_H (270MHz, $CDCl_3$) **Mixture of diastereoisomers:** 7.13-7.28 (5H, m, ArH), 5.73 **(b)** and 5.51 **(a)** (1H, ddd, *J* 18, 10, 8.5 Hz and dt, *J* 18, 9 Hz, HC=), 5.03-5.18 (2H, m, H_2C=), 3.74 and 3.62 (1H, 2 x t, *J* 7 Hz, NCH) 3.60 and 3.51 (3H, 2 x s, OCH_3), 2.64-3.33 (5H, m, NCH_2, HC-C=, $PhCH_2$), 1.58-2.02 (4H, m, 2 x CH_2). m/e (C.I.) 260, 200, 168, (E.I.) 200, 168. Exact mass (M^+ -CO_2Me) 200.1426 (Calcd. for $C_{14}H_{18}N$ 200.1438).

N-[(S)-1-(hydroxymethyl)-2-phenylethyl]-(R/S)-2-vinylpyrrolidine **(111a,b).**

υ_{max} ($CHCl_3$) 3400 cm^{-1} (br); δ_H (270MHz, $CDCl_3$) **Mixture of diastereoisomers:** 7.09-7.30 (5H, m, ArH), 5.82 **(b)** and 5.59 **(a)** (1H, 2 x dt, *J* 17.5, 8.5 Hz, HC=), 5.02-5.23 (2H, m, H_2C=), 2.33-3.60 (9H, m, 2 x NCH, NCH_2, $PhCH_2$, CH_2OH,), 1.57-2.02 (4H, m, 2 x CH_2). m/e (C.I.) 232, 200, 140 (E.I.) 200, 140. Exact mass (M^+ -CH_2OH) 200.1438 (Calcd. for $C_{14}H_{18}N$ 200.1438).

Methyl 3-methyl-(S)-2-[(R/S)-2-vinylpyrrolidin-1-yl]butanoate **(112a,b).**

υ_{max} (film) 1730, 1630 cm^{-1}; δ_H (270 MHz, $CDCl_3$) **(112a)**: 5.57 (1H, ddd, *J* 17, 10, 8 Hz, HC=), 5.15 (1H, dd, *J* 17, 2 Hz, *cis*-HC=), 5.08 (1H, dd, *J* 10, 2 Hz, *trans*-HC=), 3.68 (3H, s, OCH_3), 2.75-3.04 (4H, m, 2 x NCH, NCH_2), 1.53-2.04 (5H, m, 2 x CH_2, $HCMe_2$), 0.96 (3H, d, *J* 6.5 Hz, CH_3), 0.85 (3H, d, *J* 6.5 Hz,

CH_3). m/e (C.I.) 282, 258 (E.I.) 244, 230, 152. No analysis was obtained for this material.

N-{(R)-α-{*N*-Methyl-*N*-[(4-methylphenyl)sulphonyl](aminomethyl)}benzyl}-(S)-2-vinylpyrrolidine **(114).**

p-Toluenesulphonyl chloride (45.5mg, 1.4 eq) was added portionwise to a cooled (0°C) solution of the cyclised amine **(107a,b)** (39.2mg, 0.17 mmol) in pyridine (1ml). The reaction was stirred for 1h at 0°C then stored at -23°C overnight. Dilution of the reaction mixture with ether (20ml), washing with water (3ml), brine (3ml), drying the organic layer (Na_2SO_4) and evaporation *in vacuo* afforded a light yellow residue. Chromatography on silica gel, eluting with ethyl acetate/petrol (1:1) afforded the sulphonamide as a light yellow residue (47.4mg, 73%). This was taken-up in ether and HCl gas was bubbled through for 20 min.. The precipitated hydrochloride salt was recrystallised from dichloromethane/ethyl acetate/cyclohexane to afford the title compound as colourless crystals which were analysed by X-ray crystallography. m.p. 197°C dec.; υ_{max} 1630, 1350, 1150 cm^{-1}; proton NMR spectrum complicated by extensive overlap of signals. m/e (C.I.) 385, 186 (E.I.) 186. Exact mass (M^+-Me_2NTsCl) 186.1274 (Calcd. for $C_{13}H_{16}N$ 186.1286).

Methyl (R)-{*N*-(hexa-4,5-dienyl)-*N*-[(4-methylphenyl)sulphonyl]amino}phenylacetate **(123).**

To a solution of the ester **(89)** (87.3 mg, 0.36 mmol) in pyridine (1ml) was added *p*-toluenesulphonyl chloride (85.6mg, 1.3 eq) at 0°C, the reaction stirred for 1h and then stored at -23°C overnight. Dilution with ether (10ml), washing with aqueous hydrochloric acid (2M, 5 ml), brine (5ml), drying ($MgSO_4$) and concentration *in vacuo* afforded a yellow residue. This was chromatographed on silica gel, eluting with ether/petrol (1:2), to afford the title compound as a colourless oil (48.1mg,

34%). $[\alpha]_D^{20}$ -17.9° (c 0.48, $CHCl_3$); υ_{max} ($CHCl_3$) 1955, 1740, 1600, 1500, 1350, 1150 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8 Hz, *ortho*-ArH), 7.20-7.38 (7H, m, *meta*-ArH, PhH), 5.77 (1H, s, PhCH), 4.76 (1H, p, *J* 7 Hz, HC=), 4.52-4.58 (2H, m, H_2C=), 3.56 (3H, s, OCH_3), 3.15-3.37 (2H, m, NCH_2), 2.44 (3H, s, $ArCH_3$), 1.48-1.71 (4H, m, 2 x CH_2). m/e (C.I.) 400, 340 (E.I.) 340. Exact mass (M^+-CO_2Me) 340.1374 (Calcd. for $C_{20}H_{22}NO_2S$ 340.1370).

N-Benzylhexa-4,5-dienylamine (**125**).

To a solution of lithium aluminium hydride (530mg, 13.9 mmol) in ether (20ml) was added 4,5-hexadienitrile (550mg, 5.9 mmol) in ether (5ml) at -78°C. The reaction was warmed to room temperature over 1h, quenched with saturated aqueous sodium sulphate solution, filtered through Celite, washing with dichloromethane to afford, on evaporation *in vacuo,* 4,5-hexadienylamine as a light yellow oil (480mg).

To a solution of the crude amine (128mg, 1.3 mmol) in absolute ethanol (2ml) was added benzaldehyde (152mg, 1.1 eq) in ethanol (1ml) and the reaction stirred for 12h at room temperature. Sodium borohydride (25.2mg, 0.50 eq) was added, the reaction stirred for 10 min., diluted with water (5ml), extracted with ether (2x), dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate/petrol (1:6) afforded the title compound as a pale yellow oil, (95.1mg, 34%). υ_{max} ($CHCl_3$) 3400, 1955 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.22-7.31 (5H, m, ArH), 5.06 (1H, p, *J* 7 Hz, HC=), 4.64 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.76 (2H, s, $PhCH_2$), 2.65 (2H, t, *J* 7 Hz, NCH_2), 2.21 (1H, br s, NH), 1.99-2.04 (2H, m, H_2C-C=), 1.63 (2H, p, *J* 7 Hz, CH_2). m/e (E.I.) 187, 120, 91. Exact mass (M^+) 187.1371 (Calcd. for $C_{13}H_{17}N$ 187.1360).

N-Methyl-(R)-[2-aza-1-oxa-*cis*-7-cycloocten-2-yl]phenylacetamide (**134**).

To a solution of the cyclised amide (**105a,b**) (78.3mg, 0.32 mmol) in dichloromethane (5ml) was added *m*-chloroperbenzoic acid (85%, 67.2mg, 1.0 eq)

at 0°C over 5 min.. The reaction was stirred for 30 min. at 0°C and a solution of iron(II) sulphate heptahydrate (13.6mg, 0.15 eq) in water (0.5ml) was added, the reaction warmed to room temperature and stirred for 2h. Addition of ethylene diamine (27.3mg, 1.4 eq) and aqueous sodium hydroxide (2M, 1ml) followed by extraction with dichloromethane afforded on drying ($MgSO_4$) and evaporation, a light yellow residue. Chromatography on silica gel, eluting with ethyl acetate/petrol (2:1), afforded the title compound as a colourless oil (31.4mg, 38%). $[\alpha]_D^{25}$ -11.5° (c 0.34, $CHCl_3$); υ_{max} ($CHCl_3$) 3400, 1670 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.29-7.44 (5H, m, ArH), 6.68 (1H, br, NH), 5.73-5.85 (1H, m, HC=), 5.28-5.37 (1H, m, HC=), 4.35 (1H, s, PhCH), 4.08-4.35 (2H, m, OCH_2), 2.89 and 2.87 (3H, 2 x s, NCH_3), 2.70-2.80 (2H, m, NCH_2), 2.24-2.35 (2H, m, H_2C-C=), 1.64-1.73 (2H, m, CH_2). m/e (C.I.) 261, 202, 150, 112 (E.I.) 202, 112. Exact mass (M^+ -CONHMe) 202.1223 (Calcd. for $C_{13}H_{16}NO$ 202.1230).

Methyl (R)-2-{*N*-[4-chloro-(R)-1-vinylbutyl]-*N*-[2,2,2-trichloroethyloxycarbonyl]amino} phenylacetate **(137).**

To a solution of the cyclised ester **(104b)** (32.0mg, 0.13 mmol) in chlorobenzene (1ml) was added 2,2,2-trichloroethyl chloroformate (22µl, 1.2 eq) and the reaction heated to reflux for 4h. Dilution with ether (10ml), washing with aqueous hydrochloric acid (2M, 2ml), drying ($MgSO_4$) and concentration *in vacuo* afforded, after purification by preparative plate chromatography, the title compound as a colourless oil (13.3mg, 22%). $[\alpha]_D^{25}$ -54.0° (c 0.20, $CHCl_3$); υ_{max} ($CHCl_3$) 1730, 1700, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.27-7.44 (5H, m, ArH), 5.87 (1H, s, PhCH), 5.59 (1H, ddd, *J* 17, 10, 8 Hz, HC=), 5.15 (1H, d, *J* 17 Hz, *cis*-HC=), 5.05 (1H, d, *J* 10 Hz, *trans*-HC=), 4.86 (1H, d, *J* 12 Hz, OCH), 4.77 (1H, d, *J* 12 Hz, OCH), 4.05-4.13 (1H, m, HC-C=), 3.79 (3H, s, OCH_3), 3.28-3.43 and 3.07-3.20 (2H, 2 x m, CH_2Cl), 1.46-1.64 (3H, m, HCH_2), 1.76-1.84 (1H, m, $\underline{H}CH_2$). m/e (C.I.) 460, 458, 456, 424, 422, 420, 400, 398, 396, 205, 149 (E.I.) 400, 398,396,

149. Exact mass (M^+-CO_2Me) 396.0063 (Calcd. for $C_{16}H_{18}NO_2\ ^{35}Cl_4$ 396.0089).

N-{(R/S)-[*N*-(hepta-5,6-dienyl)amino]phenyl}acetyl pyrrolidine **(140).**

To a solution of the alcohol **(138)** (745mg, 6.7 mmol) in DMSO (20ml) was added triethylamine (5.3ml, 5.8 eq) and a solution of pyridine-sulphur trioxide complex in DMSO (3.0g, 2.9 eq in 10ml) at room temperature. The reaction was stirred for 30 min., diluted with water (50ml) and then extracted with ether/30-40° petrol (1:1), (3x50ml), washed with water (3x20ml), dilute aqueous hydrochloric acid (3x20ml) and dried ($MgSO_4$). To the solution was added a solution of the amino amide **(139)** (1.26g, 0.92 eq) in dichloromethane (10ml) and the reaction stirred at room temeperature over magnesium sulphate and 4Å molecular sieves. After 45 min., the reaction was filtered, concentrated *in vacuo*, taken up in absolute ethanol (100ml) and sodium borohydride (125mg, 0.50 eq) was added. The reaction was stirred for 2h, diluted with water (50ml) extracted with ether (3x), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate/petrol (3:1), yielded the title compound as a light yellow oil (640 mg, 32%). υ_{max} ($CHCl_3$) 3450, 1960, 1630 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.25-7.39 (5H, m, ArH), 5.06 (1H, p, *J* 7 Hz, HC=), 4.62 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 4.34 (1H, s, PhCH), 3.36-3.62 and 3.12-3.20 (6H, 2 x m, 3 x NCH_2), 2.37-2.59 (3H, m, H_2C-C=, NH), 1.74-2.02 (4H, m, 2 x ring CH_2), 1.38-1.58 (4H, m, 2 x CH_2); δ_C (68 MHz, $CDCl_3$) 170.38 (s), 138.50 (s), 128.60 (d), 127.73 (d), 127.60 (d), 89.68 (d), 74.47 (t), 64.45 (d), 47.32 (t), 45.83 (t), 45.77 (t), 29.48 (t), 27.96 (t), 26.63 (t), 25.82 (t), 23.84 (t). Allene C singlet not observed. m/e (C.I.) 299, 200. Exact mass (MH^+) 299.2123 (Calcd. for $C_{19}H_{27}N_2O$ 299.2123).

N-[(R/S)-2-(hepta-5,6-dienyl)amino-2-phenylethyl]pyrrolidine **(141).**

To a solution of the allenic amide **(140)** (272mg, 1.07 mmol) in THF (20ml) was added a solution of DiBAl in toluene (1.5M, 2.0ml, 3.2 eq) at room temperature

and the reaction stirred for 20 min.. Quenching with saturated aqueous ammonium chloride solution was followed by filtration through Celite, washing with dichloromethane. Evaporation *in vacuo* and chromatography on silica gel, eluting with dichloromethane/methanol/ammonia (90:10:1), afforded the title compound as a colourless oil (120mg, 46%). υ_{max} ($CHCl_3$) 3300, 1955, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.24-7.46 (5H, m, ArH), 5.07 (1H, p, *J* 7 Hz, HC=), 4.63 (2H, dt, *J* 7, 3.5 Hz, H_2C=), 3.71 (1H, dd, *J* 11, 3.5 Hz, PhCH), 2.83 (1H, dd, *J* 12, 11 Hz, PhC-CH), 2.57-2.62 (2H, m, NCH_2), 2.44-2.49 (4H, m, 2 x ring NCH_2), 2.27 (1H, dd, *J* 12, 3.5 Hz, PhC-CH), 2.15 (1H, br s, NH), 1.97 (2H, qt, *J* 7, 3.5 Hz, H_2C-C=), 1.73-1.80 (4H, m, 2 x ring CH_2), 1.36-1.57 (4H, m, 2 x CH_2); δ_C (68 MHz, $CDCl_3$) 208.53 (s), 143.36 (s), 128.28 (d), 127.4 (d), 126.98 (d), 89.88 (d), 74.54 (t), 63.90 (d), 62.18 (t), 54.10 (t), 47.78 (t), 29.65 (t), 28.15 (t), 26.89 (t), 23.61 (t). m/e (C.I.) 285, 200, 84. (E.I.) 200, 84. Exact mass (M^+-$CH_2NC_4H_8$ 200.1426) (Calcd. for $C_{14}H_{18}N$ 200.1439).

N-{(R/S)-Phenyl[(R/S)-2-vinylpiperidin-1-yl]}acetyl pyrrolidine **(142a,b).**

Prepared by general procedure (B).

(142a): υ_{max} ($CHCl_3$) 1630 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.29-7.37 (5H, m, ArH), 6.00 (1H, ddd, *J* 18, 10, 8.5 Hz, HC=), 5.21 (1H, dd, *J* 18, 1.5 Hz, *cis*-HC=), 5.20 (1H, dd, *J* 10, 1.5 Hz, *trans*-HC=), 4.82 (1H, s, PhCH), 3.34-3.60 (4H, m, 2 x pyrrolidine NCH_2), 2.42-2.63, 2.82-2.89 and 2.95-3.03 (3H, 3 x m, 3 x NCH), 1.55-1.94 (10H, m, 5 x CH_2); δ_C (68 MHz, $CDCl_3$) 170.25 (s), 141.90 (d), 133.96 (s), 130.03 (d), 127.96 (d), 127.50 (d), 116.34 (t), 65.78 (d), 63.93 (d), 48.68 (t), 46.09 (t), 45.96 (t), 33.99 (t), 26.11 (t), 25.82 (t), 23.90 (t), 23.48 (t); m/e (C.I.) 299, 200, 83. (E.I.) 200, 83. Exact mass (M^+-COC_4H_8N) (Calcd. for $C_{14}H_{18}N$).

N-[(R/S)-α-(pyrrolidin-1-ylmethyl)benzyl]-(R/S)-2-vinylpiperidine **(143a,b).**

Prepared by general procedure (B).

υ_{max} ($CHCl_3$) 1630, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) **Mixture of diastereomers:**

7.18-7.40 (5H, m,ArH), 5.84-6.07 (1H, m, HC=), 5.25, 5.24, 5.22 and 5.08 (2H, d, *J* 16 Hz, *cis*-HC= (**a**); d, *J* 11 Hz, *trans*-HC= (**a**); d, *J* 16 Hz, *cis*-HC= (**b**); d, *J* 11 Hz, *trans*-HC= (**b**)), 4.40 and 4.15 (1H, dd, *J* 8, 5.5 Hz, PhCH (**a**); dd, *J* 10, 4 Hz, PhCH (**b**)), 2.00-3.25 (9H, m, 9 x NCH), 1.38-1.85 (10H, m, 5 x CH_2); m/e (C.I.) 285, 200. (E.I.) 200. Exact mass (MH^+) 299.1213 (Calcd. for $C_{19}H_{27}N_2O$ 299.1213).

General procedure (C) for palladium(II)-mediated cyclisations under carbomethoxylation conditions.

To a 0.5M solution of the appropriate allenic amine in dry methanol was added the palladium(II) catalyst (see Tables in text for catalyst used and molar proportion) and anhydrous copper(II) chloride (3 equivalents). The dark green reaction mixture was stirred under an atmosphere of carbon monoxide at room temperature until the conversion was complete, as indicated by t.l.c.. Water and ether were then added followed by addition of excess ethanolamine. The ether layer was separated and the blue aqueous layer extracted twice more with ether. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The mixture was analysed by proton NMR and where necessary or appropriate, the product was further purified and/or the diastereoisomers separated by silica gel chromatography.

Methyl 2-{(R)-N-[(S)-α-methylbenzyl]pyrrolidin-2-yl}propenoate **(144a)** and Methyl 2-{(S)-N-[(S)-α-methylbenzyl]pyrrolidin-2-yl}propenoate **(144b)**

(144a): $[\alpha]_D^{25}$ +41.0° (c 4.5, $CHCl_3$); υ_{max} (film) 1710, 1630, 1500 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.18-7.40 (5H, m, ArH), 6.14 (1H, d, *J* 2 Hz, *cis*-HC=), 6.02 (1H, dd, *J* 2, 1 Hz, *trans*-HC=), 3.70 (3H, s, OCH_3), 3.72-2.82 (2H, m, HC-C=, PhCH), 2.85-2.92 (1H, m, NCH), 2.61 (1H, q, *J* 8 Hz, NCH), 2.01-2.18 (1H, m, $\underline{H}CH_2$), 1.60-1.78 (2H, m, 2 x $\underline{H}CH_2$), 1.42-1.59 (1H, m, $\underline{H}CH_2$), 1.27 (3H, d, *J* 7

Hz, CH_3); δ_C (68MHz, $CDCl_3$) 167.56 (s), 144.63 (s), 143.95 (s), 127.90 (s), 127.60 (s), 126.47 (s), 124.55 (t), 60.46 (d), 58.91 (d), 51.45 (q), 48.46 (t), 33.15 (t), 23.36 (t), 15.47 (q). **(144b)**: $[\alpha]_D^{25}$ -40.5° (c 4.5, $CHCl_3$); υ_{max} (film) 1710, 1630, 1500 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.18-7.40 (5H, m, ArH), 6.30 (1H, d, *J* 2 Hz, *cis*-HC=), 6.28 (1H, dd, *J* 2, 1 Hz, *trans*-HC=), 3.77 (3H, s, OCH_3), 3.67-3.82 (1H, m, HC-C=), 3.62 (1H, q, *J* 7 Hz, PhCH), 2.85-2.92 and 2.19-2.28 (2H, 2 x m, NCH_2), 2.07 (1H, p, *J* 7 Hz, $\underline{H}CH_2$), 1.46-1.72 (3H, m, HCH_2), 1.35 (3H, d, *J* 7 Hz, CH_3); δ_C (68MHz, $CDCl_3$) 167.62 (s), 145.54 (s), 144.27 (s), 128.05 (d), 127.60 (d)., 126.69 (d), 124.55 (t), 62.92 (d), 60.00 (d), 52.19 (t), 51.54 (q), 33.38 (t), 23.26 (q), 23.16(t). **(144a/144b)**: m/e (E.I.) 259, 244, 154. Exact mass (M^+) 259.1570 (Calcd. for $C_{16}H_{21}NO_2$ 259.1570).

Methyl 2-{(R/S)-*N*-[(R)-α-(methoxycarbonyl)benzyl]pyrrolidin-1-yl}propenoate **(145a,b)**

Procedure (i): General procedure (C).

Procedure (ii):

To a solution of the allenic ester **(89)** (29.9mg, 0.12mmol) in THF (3ml) was added mercuric acetate (38.3mg, 0.98 eq) and the reaction stirred at room temperature for 30min.. Sodium carbonate (14.9mg, 1.2eq) was added and the reaction stirred for a further 30min.. Concentration *in vacuo* followed by addition of dichloromethane and filtration afforded on further concentration *in vacuo*, the alkenylmercuric acetate as a light yellow oil. This was dissolved in methanol (5ml), lithium chloride (11.9mg, 2.5eq) and palladium(II) chloride (21.2mg, 1.1eq) were added and the reaction stirred at room temperature, under an atmosphere of carbon monoxide overnight. Dilution with ether (10ml), addition of activated charcoal and stirring for 20min. was followed by filtration through Celite and concentration *in vacuo*. Chromaography on silica gel, eluting with dichloromethane afforded the title compound as a colourless oil, (21.3mg, 58%). υ_{max}($CHCl_3$) 1730, 1625 cm^{-1}; δ_H (270MHz, $CDCl_3$) **Mixture of**

diastereoisomers: 7.29-7.38 (5H, m, ArH), 6.21 **(a)** and 6.24 **(b)** (1H, 2 x d, *J* 2 Hz, *cis*-HC=), 6.05 **(a)** and 6.07 **(b)** (1H, 2 x dd, *J* 2, 1 Hz, *trans*-HC=), 4.55 **(a)** and 4.47 **(b)** (1H, 2 x s, PhCH), 3.80-3.92 (1H, m, NCH), 3.74 **(a/b)**, 3.72 **(a)** and 3.63 **(b)** (6H, 3 x s, 2 x OCH_3), 2.34-2.45, 2.78-2.87 and 3.03-3.18 (2H, 3 x m, NCH_2), 1.99-2.28 (1H, m, $\underline{H}CH_2$), 1.48-1.81 (3H, m, HCH_2). m/e (C.I.) 304, 244 (E.I.) 244. Exact mass (M^+ -CO_2Me) 244.1362 (Calcd. for $C_{15}H_{18}NO_2$) 244.1337.

Methyl 2-{(R/S)-*N*-{(R)-α-[*N*-methylcarbamoyl]benzyl}pyrrolidin-2-yl}propenoate **(146a,b).**

υ_{max} ($CHCl_3$) 3400, 1710, 1665, 1620 cm^{-1}; δ_H (270MHz, $CDCl_3$). **Mixture of diastereoisomers**: 7.17-7.38 (5H, m, ArH), 6.78 (1H, br s, NH), 6.34 **(b)** and 6.06 **(a)** (1H, 2xd, *J* 2 Hz, *cis*-HC=), 5.91 **(b)** and 5.74 **(a)** (1H, 2 x dd, *J* 2, 1 Hz, *trans*-HC=), 4.33 **(b)** and 4.19 **(a)** (1H, 2 x s, PhCH), 3.78 **(b)** and 3.65 **(a)** (3H, 2 x s, OCH_3) 3.43-3.78 (1H, m, HC-C=), 3.13-3.19 and 2.70-2.91 (2H, 2 x m, NCH_2), 2.86 **(a)**, 2.84 **(a/b)**, 2.82 **(b)** (3H, 3 x s, NCH_3), 1.94-2.18 (1H, m, $\underline{H}CH_2$), 1.52-1.83 (3H, m, HCH_2). m/e (C.I.) 303, 244. (E.I.) 244. Exact mass (M^+ -CONHMe) 244.1326. (Calcd. for $C_{15}H_{18}NO_2$ 244.1337).

Methyl 2-{(R/S)-*N*-[(R)-α-(hydroxymethyl)benzyl]pyrrolidin-2-yl}propenoate **(147a,b).**

υ_{max} ($CHCl_3$) 3400 (br), 1720, 1650; δ_H (270MHz, $CDCl_3$) **Less polar diastereoisomer**: 7.15-7.39 (5H, m, ArH), 6.34 (1H, d, *J* 2 Hz, *cis*-HC=), 6.01 (1H, dd, *J* 2, 0.5 Hz, *trans*-HC=), 3.57-3.99 (4H, m, PhCH, OCH_2, HC-C=), 3.79 (3H, s, OCH_3), 2.97-3.05 (1H, m, NCH), 2.23-2.32 (1H, m, NCH), 1.58-2.02 (5H, m and br s, 2 x CH_2, OH); **More polar diastereoisomer**; 7.27-7.35 (5H, m, ArH), 6.15 (1H, d, *J* 2 Hz, *cis*-HC=), 5.89 (1H, dd, *J* 2, 1 Hz, *trans*-HC=), 3.74-3.90 (4H, m, PhCH, HC-C=, OCH_2), 3.70 (3H, s, OCH_3), 3.17-3.23 (1H, m, NCH), 2.73-2.83 (1H, m, NCH), 1.58-1.88 (5H, m and br s, 2 x CH_2, OH). **(147a,b)**: m/e (C.I.) 276,

244 (E.I.) 244. Exact mass (M^+ -CH_2OH) 244.1314 (Calcd. for $C_{15}H_{18}NO_2$ 244.1337).

Methyl (R/S)-2-{*N*-[(S)-1-(methoxycarbonyl)-2-phenylethyl]pyrrolidin-2-yl}propenoate **(148a,b).**

υ_{max} ($CHCl_3$) 1730, 1715, 1620 cm^{-1}; δ_H (270MHz, $CDCl_3$) **Mixture of diastereoisomers:** 7.11-7.38 (5H, m, ArH), 6.22 **(a)**, 5.99 **(a)**, 5.93 **(b)**, 5.21 **(b)**, (2H, 4 x dd, *J* 2, 1 Hz, H_2C=), 2.79-4.13 (6H, m, $PhCH_2$, 2 x NCH, NCH_2), 3.76 **(b)**, 3.69 **(a)**, 3.66 **(a)**, 3.57 **(b)**, (6H, 4 x s, 2xOCH_3), 2.03-2.21 (1H, m, $\underline{H}CH_2$), 1.40-1.79 (3H, m, HCH_2). m/e (C.I.) 318, 258, 226. (E.I.) 258, 226. Exact mass (M^+ -CO_2Me) 258.1471 (Calcd. for $C_{16}H_{20}NO_2$ 258.1492).

Methyl (R/S)-2-{*N*-[(S)-1-(methoxymethyl)-2-phenylethyl]pyrrolidin-1-yl}propenoate **(149a,b).**

Less polar diastereoisomer: $[\alpha]_D^{25}$ -35.0° (c 0.04, Et_2O); υ_{max} ($CHCl_3$) 1710, 1630, 1600 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.16-7.26 (5H, m, ArH), 5.93 (1H, s, *cis*-HC=), 5.31 (1H, s, *trans*-HC=), 3.88-3.96 (1H, m, HC-C=), 3.70 (3H, s, CO_2CH_3), 3.35-3.48 (2H, m, OCH_2), 3.28 (3H, s, OCH_3), 3.09-3.18 (1H, m, NCH), 2.65-3.01 (4H, m, NCH_2, $PhCH_2$), 2.00-2.14 (1H, m, $\underline{H}CH_2$), 1.57-1.74 (2H, m, 2 x $\underline{H}CH_2$), 1.37-1.49 (1H, m, $\underline{H}CH_2$). m/e (C.I.) 304, 258, 212 (E.I.) 258, 212. Exact mass (M^+ -CH_2OMe) 258.1501 (Calcd. for $C_{16}H_{20}NO_2$ 258.1492).

Methyl (S)-2-{(R/S)-2-[1-methoxycarbonyl)vinyl]pyrrolidin-1-yl}-3-methylbutanoate **(150a,b).**

υ_{max} ($CHCl_3$) 1715, 1620 cm^{-1}; δ_H (270 MHz, $CDCl_3$) **(150a)**: 6.22 (1H, d, *J* 2 Hz, *cis*-HC=), 5.94 (1H, dd, *J* 2, 1.5 Hz, *trans*-HC=), 3.75 and 3.67 (6H, 2 x s, 2 x

OCH_3), 3.59-3.69 (1H, m, HC-C=), 2.98-3.03 (2H, m, NCH_2), 2.88 (1H, d, *J* 10.5 Hz, NCH), 1.49-2.12 (5H, m, 2 x CH_2, $HCMe_2$), 1.03 (3H, d, *J* 7 Hz, CH_3), 0.85 (3H, d, *J* 6.5 Hz, CH_3). **(150a,b)**: m/e (C.I.) 270, 226, 210 (E.I.) 226, 210. Exact mass (M^+-CO_2Me) 210.1491. (Calcd. for $C_{12}H_{20}NO_2$ 210.1494).

Methyl (R/S)-2-{*N*-[(S)-1-(hydroxymethyl)-2-phenylethyl]pyrrolidin-1-yl}propenoate **(151a,b).**

υ_{max} ($CHCl_3$) 3400 (br), 1705, 1620 cm^{-1}; δ_H (270MHz, $CDCl_3$). **Mixture of diastereoisomers**: 7.08-7.30 (5H, m, ArH), 6.24 **(b)**, 6.18 **(a)**, 5.80 **(a)**, 5.76 **(b)** (2H, 4 x s, H_2C=), 2.42-4.08 (9H, m, $PhCH_2$, CH_2OH, CH_2N, 2 x NCH), 3.76 (3H, s, OCH_3), 1.60-2.20 (4H, m, 2 x CH_2). m/e (C.I.) 290, 258, 196. Exact mass (MH^+) 290.178 (Calcd. for $C_{17}H_{24}NO_3$ 290.176).

Methyl 3-methyl-(R)-5-phenyl-(R/S)-octahydropyrrolo[1,2-d][1,4]diazepine-(9a R/S)-1-carboxylate **(153a-d).**

Major diastereoisomer: υ_{max} ($CHCl_3$) 1725, 1600 cm^{-1}; δ_H (270MHz, $CDCl_3$): 7.19-7.34 (5H, m, ArH), 3.72 (3H, s, OCH_3), 3.52 (1H, dd, *J* 9, 4 Hz, PhCH), 3.23-3.33 (1H, m, NCH), 2.57-2.99 (6H, m, 3 x NCH_2), 2.35 (3H, s, NCH_3), 1.97-2.14 (3H, m, HCO_2Me, 2 x $\underline{H}CH_2$), 1.57-1.70 (2H, m, 2 x $\underline{H}CH_2$). m/e (C.I.) 289. (E.I.) 230, 147, 104. Exact mass (M^+- CH_2NMe_2) 230.1195 (Calcd. for $C_{14}H_{16}NO_2$ 230.1180).

Methyl 2-{(R/S)-*N*-[(R/S)-α-(allyloxycarbonyl)benzyl]pyrrolidin-2-yl}propenoate **(154a,b).**

υ_{max} ($CHCl_3$) 1715, 1705, 1620, 1595; δ_H (270 MHz, $CDCl_3$) **Less polar diastereoisomer**: 7.28-7.35 (5H, m, ArH), 6.25 (1H, s, *cis*-HC=), 6.08 (1H, s, *trans*-HC=), 5.81-5.97 (1H, m, HC=), 5.18-5.31 (2H, m, H_2C=), 4.65 (2H, d, *J* 5.5 Hz, OCH_2), 4.57 (1H, s, PhCH), 3.89-3.94 (1H, m, HC-C=), 3.74 (3H, s, OCH_3),

3.04-3.25 (1H, m, NCH), 2.80-2.90 (1H, m, NCH), 2.17-2.29 (1H, m, $\underline{H}CH_2$), 1.55-1.72 (3H, m, HCH_2); **More polar diastereoisomer**: 7.29-7.36 (5H, m, ArH), 6.21 (1H, s, *cis*-HC=), 6.07 (1H, s, *trans*-HC=), 5.77-5.90 (1H, m, HC=), 5.13-5.31 (2H, m, H_2C=), 4.52-4.69 (2H, m, OCH_2), 4.49 (1H, s, PhCH), 3.84-3.91 (1H, m, HC-C=), 3.74 (3H, s, OCH_3), 3.08-3.17 (1H, m, NCH), 2.36-2.47 (1H, m, NCH), 2.01-2.16 (1H, m, $\underline{H}CH_2$), 1.48-1.78 (3H, m, HCH_2). **(154a,b)**: m/e (C.I.) 330, 244 (E.I.) 244. Exact mass (M^+-$CO_2C_3H_5$) 244.1335 (Calcd. for $C_{15}H_{18}NO_2$ 244.137).

Methyl (R)-phenyl[(R/S)-2-vinylpyrrolidin-1-yl]acetate dimer **(163).**

To a solution of the methyl ester **(89)** (40.4mg, 0.16 mmol) in methanol (4ml) was added copper(II) chloride (67.1mg, 3.1 eq), palladium(II) chloride, (R)-(+)-BINAP (7.1 mg, 0.06 eq) and the reaction heated to reflux for 30 min. under an atmosphere of carbon monoxide. Dilution with ether (10ml), water (5ml) and addition of excess ethanolamine, followed by separation of the organic layer, drying ($MgSO_4$) and evaporation *in vacuo* afforded a yellow residue. Chromatography on silica gel, eluting with ethyl acetate/petrol (1:9), afforded the title compound (major component) as a colourless oil (5.5 mg, 14%). **Major diastereoisomer**: υ_{max} 1735, 1605 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 7.26-7.34 (10H, m, ArH), 5.44 and 5.22 (4H, 2 x s, 2 x H_2C=), 4.62 (2H, s, 2 x PhCH), 3.73 (2H, d, *J* 7 Hz, 2 x HC-C=), 3.67 (6H, s, 2 x OCH_3), 3.45-3.50 and 3.26-3.31 (4H, 2 x m, 2 x NCH_2), 2.26-2.35 (2H, m, 2 x $\underline{H}CH_2$), 1.46-1.93 (6H, m, 2 x HCH_2). m/e (C.I.) 489, 429, 339. Exact mass (MH^+) 489.274 (Calcd. for $C_{30}H_{37}N_2O_4$ 489.275).

Allyl (R/S)-[*N*-allyl-*N*-(hexa-4,5-dienyl)amino]phenylacetate **(167).**

To a solution of the allenic ester **(110)** (62.5mg, 0.23mmol) in dry, degassed methanol (4ml) was added tetrakis(triphenylphosphine)palladium(0) (14.5mg, 0.05eq) and the reaction allowed to stir under an atmosphere of carbon monoxide. After 1h, the yellow colour of the reaction mixture faded and a further portion of

catalyst (9.7mg, 0.03eq) was added. The reaction was continued for a further 30 min., concentrated *in vacuo*, diluted with dichloromethane, filtered and evaporated to afford a light yellow oil. Chromatography on silica gel, eluting with ethyl acetate/petrol (1:1) afford the title compound as a colourless oil (8.7mg, 12%). υ_{max} ($CHCl_3$) 1955, 1730, 1640, 1660 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.31-7.47 (5H, m, ArH), 5.74-5.97 (2H, m, 2 x HC=), 5.08-5.32 (4H, m, H_2C=), 5.02 (1H, p, *J* 7 Hz, HC==), 4.59-4.66 (5H, m, H_2C==, PhCH, OCH_2), 3.17-3.28 (2H, br, NCH_2-C=), 2.53-2.68 (2H, br, NCH_2), 1.82-2.04 (2H, m, H_2C-C==), 1.50-1.67 (2H, m, CH_2). m/e (C.I.) 312, 226. Exact mass (MH^+) 312.1960 (Calcd for $C_{20}H_{26}NO_2$ 312.1964).

Ethyl 4-{(S)-*N*-[(S)-α-methylbenzyl]pyrrolidin-2-yl}-4-pentenoate **(170)** and Ethyl 4-{(R)-*N*-[(S)-α-methylbenzyl]pyrrolidin-2-yl}-4-pentenoate *epi*-**(170)**

To a solution of the alcohol **(188)**/*epi*-**(188)** (8.15 g, 35 mmol) in triethyl orthoacetate (150 ml) was added trimethylacetic acid (catalytic) and the reaction heated to 155°C, with a Claisen head and receiver attached, to collect ethanol produced in the reaction. After 1h the reaction was cooled, the solvent evaporated *in vacuo* and the residue diluted in ethyl acetate (30ml), washed with saturated aqueous sodium bicarbonate (10ml), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on flash silica, eluting with ethyl acetate/petrol (1:2), afforded recovered **(188)**/*epi*-**(188)** (1.08g) and the title compound as a light yellow oil (8.72g, 95% based on **(188)**/*epi*-**(188)**). **(170)**: $[\alpha]_D^{22}$ -23.2° (c 0.17, $CHCl_3$); υ_{max} (film) 1720, 1640, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.20-7.34 (5H, m, ArH), 5.18 and 4.84 (2H, 2 x s, 2 x HC=), 4.16 (2H, q, *J* 7 Hz, OCH_2), 3.72 (1H, q, *J* 7 Hz, PhCH), 2.95-3.03 (2H, m, HC-C=, NCH), 2.31-2.60 (4H, m, $COCH_2$, H_2C-C=), 2.13-2.22 (1H, m, NCH), 1.48-1.88 (4H, m, 2 x CH_2), 1.39 (3H, d, *J* 7 Hz, PhC-CH_3), 1.27 (3H, t, *J* 7 Hz, COC-CH_3); δ_C (68 MHz, $CDCl_3$) 173.46 (s), 151.31 (s), 141.94 (s), 128.15 (d), 127.79 (d), 126.63 (d), 109.60 (t), 66.07 (d), 60.23 (t), 59.81 (d), 49.07 (t), 32.73 (t), 31.49 (t), 26.56 (t), 22.93 (t), 21.47 (q),

14.21 (q). *epi*-**(170)** : $[\alpha]_D^{20}$ +23.4 (c 0.18, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 7.16-7.37 (5H, m, ArH), 5.02 and 4.68 (2H, 2 x s, H_2C=), 4.12 (2H, q, *J* 7 Hz, OCH_2), 3.85 (1H, q, *J* 6.5 Hz, PhCH), 3.25-3.31 (1H, m, NCH), 2.74-2.82 (1H, m, HC-C=), 2.25-2.53 (5H, m, NCH, $COCH_2$, H_2C-C=), 1.62-1.93 (4H, m, 2 x CH_2), 1.30 (3H, d, *J* 6.5 Hz, PhC-CH_3), 1.24 (3H, t, *J* 7 Hz, COC-CH_3); δ_C (68 MHz, $CDCl_3$) 173.53 (s), 144.89 (s), 128.22 (s), 127.86 (d), 127.60 (d), 126.34 (d), 109.99 (t), 66.78 (d), 60.23 (t), 56.96 (d), 47.06 (t), 32.70 (t), 31.14 (t), 25.92 (t), 23.26 (t), 14.24 (q), 13.01 (q). **(170)**/*epi*-**(170)**: m/e (E.I.) 301, 286, 196, 174. Exact mass (M^+) 301.2039 (Calcd. for $C_{19}H_{27}NO_2$ 301.2039).

N-Benzyl-(R/S)-2-vinylpyrrolidine dimer **(171a,b).**

To a solution of the allene **(125)** (9.6mg, 0.05 mmol) in dichloromethane (2ml) was added copper(I) chloride (2.5mg, 0.51 eq) and the reaction stirred for 5h at room temperature. Dilution with dilute aqueous ammonia followed by extraction with ethyl acetate (2x) and drying (Na_2SO_4) afforded, on evaporation *in vacuo* and preparative plate chromatography, three components; **(171a)** (1.6mg), **(171b)** (1.2 mg) and **(126)** (1.4 mg), in a yield of 34% based on **(126)**. **(171b)**: υ_{max} ($CHCl_3$) 1655, 1600, 1500 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31-7.33 (10H, m, ArH), 5.53 and 5.31 (4H, 2 x s, 2 x H_2C=), 4.01 (2H, 2 x d, *J* 13 Hz, 2 x PhCH), 3.22 (2H, 2 x d, *J* 13 Hz, 2 x PhCH), 3.13-3.20 (2H, m, 2 x NCH), 2.97-3.02 (2H, m, 2 x NCH), 2.18-2.29 (2H, m, 2 x NCH), 1.67-2.04 (8H, m, 4 x CH_2); **(171a)**: υ_{max} ($CHCl_3$) 1655, 1600, 1500 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.28-7.33 (10H, m, ArH), 5.61 and 5.34 (4H, 2 x s, 2 x H_2C=), 4.09 (2H, d, *J* 15 Hz, 2 x PhCH), 3.18-3.28 (2H, m, 2 x NCH), 3.08 (2H, d, *J* 15 Hz, 2 x PhCH), 2.99-3.11 (2H, m, 2 x NCH), 2.07-2.18 (2H, m, 2 x NCH), 1.60-1.80 (8H, m, 4 x CH_2). **(171a,b)**: m/e (E.I.) 372, 281, 212, 160, 149. 91. No analysis was obtained for this material.

(S/R)-1-{*N*-[(R)-α-(methoxycarbonyl)benzyl]pyrrolidin-2-yl}vinylmercuric chloride **(175a,b).**

To a solution of the allenic ester (**89**) (63.5mg, 0.26 mmol) in THF (3ml) was added mercuric chloride (72mg, 1.0eq) and the reaction stirred for 1h. Sodium carbonate (33.6mg, 1.2eq) was added and the reaction stirred for a further hour after which time concentration *in vacuo*, dilution with dichlormethane, filtration and chromatography on silica gel, eluting with petrol/ethyl acetate (4:1) afforded the title compound as a colourless oil (82.2mg, 66%). υ_{max} ($CHCl_3$) 1725, 1605 cm^{-1}. δ_H (270MHz, $CDCl_3$) **Mixture of diastereoisomers**: (Satellites due to ^{199}Hg-^1H coupling not included) 7.30-7.44 (5H, m, ArH), 5.62 (**a**) and 5.58 (**b**) (1H, 2 x d, *J* 1 Hz, *cis*-HC=), 5.00 (**a**) and 4.99 (**b**) (1H, 2 x s, *trans*-HC=), 4.64 (**a**) and 4.32 (**b**) (1H, 2 x s, PhCH), 3.74 (**a**) and 3.64 (**b**) (3H, 2 x s, OCH_3), 3.50-3.56 (**a**) and 3.34-3.39 (**b**) (1H, 2 x m, HC-C=), 2.83-3.09 and 2.02-2.34 (2H, 2xm, NCH_2), 2.06-2.17 (1H, m, $\underline{H}CH_2$), 1.56-1.86 (3H, m, HCH_2). m/e (C.I.) 484, 482, 480, 424, 422, 420, 244 (E.I.) 466, 464, 422, 420, 419. Exact mass (M^+ -CO_2Me) 422.0585 (Calcd. for $C_{13}H_{15}N^{35}Cl^{202}Hg$ 422.0597).

<u>(S)-1-{*N*-[(R)-α-(*N*-methylcarbamoyl)benzyl]pyrrolidin-2-yl}vinylmercuric chloride (**176a**).</u>

To a solution of the allenic amide (**90**) (48.2mg, 0.2mmol) in THF (5ml) was added mercuric chloride (56.1mg, 1.0eq) and the reaction stirred for 20 min.. Sodium carbonate (29.9mg, 1.4eq) was added, the reaction stirred for a further 10min., concentrated *in vacuo*, diluted with dichloromethane (10ml), washed with water (5ml) the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel, eluting with petrol/ethyl acetate (3:2) afforded the title compound as a colourless oil, (67.5mg, 70%). υ_{max} ($CHCl_3$) 3400, 1660, 1610 cm^{-1}; δ_H (270MHz, $CDCl_3$) (Corresponding shifts of selected signals for (**176b**) indicated in italics and satellites due to ^{199}Hg-^1H coupling not included) 7.16-7.39 (5H, m, ArH), 6.97 (1H, br s, NH), 5.80 *(5.28)* (1H, s, *cis*-HC=), 5.20 *(4.67)* (1H, s, *trans*-HC=), 4.44 *(4.32)* (1H, s, PhCH), 3.28 *(3.33)* (1H, t, *J* 7.5 Hz, HC-C=), 3.78 and 3.80 (3H, 2 x s, NCH_3), 2.71-2.79 (1H, m, NCH), 1.52-2.17 (5H, m, NCH, 2 x

CH_2). m/e (C.I.) 483, 481, 479, 424, 422, 420, 243 (E.I.) 420, 422, 424, 243. Exact mass (M^+ -CONHMe) 422.0557 (Calcd. for $C_{13}H_{15}N\ ^{35}Cl\ ^{202}Hg$ 422.0597).

3-Methyl-1-methylene-(R)-5-phenyl-(9a R/S)-octahydropyrrolo[1,2-d][1,4]diazepine-2,4-dione **(177).**

To a solution of the allenic amide (**90**) (78.5mg, 0.32mmol) in THF (15ml) was added mercuric chloride (88.2mg, 1 eq) and the reaction was stirred for 15 min.. Sodium carbonate (39.0mg, 1.1 eq) was added and the reaction stirred for a further 10 min.. Concentration *in vacuo*, followed by dilution in dichloromethane afforded a suspension which was filtered and the filtrate concentrated *in vacuo* to afford the crude alkenylmercuric chloride. This was dissolved in dry methanol (5ml), lithium chloride (38.5mg, 2.8 eq) and palladium(II) chloride (62.1mg, 1.1 eq) were added and the reaction stirred overnight under an atmosphere of carbon monoxide. The reaction mixture was filtered through Celite, concentrated *in vacuo*, the residue dissolved in dichloromethane, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate/petrol (3:2) afforded two components; the minor diastereoisomer of the expected product (**146b**) (19.3mg, 20%) and the more polar title compound as a colourless oil (8.0mg, 9%). υ_{max} ($CHCl_3$) 1710, 1650 cm^{-1}; δ_H (270MHz, $CDCl_3$) **6.7:1 Mixture of diastereoisomers**: 7.30-7.37 (5H, m, ArH), 5.95 *(minor)* and 5.89 *(major)* (1H, 2 x s, *cis*-HC=), 5.52 *(minor)* and 5.16 *(major)* (1H, 2 x s, *trans*-HC=), 5.01 *(minor)* and 4.70 *(major)* (1H, 2 x s, PhCH), 4.06-4.19 (1H, m, HC-C=), 3.29 *(major)* and 3.26 *(minor)* (3H, 2 x s, NCH_3), 2.94-3.03 (1H, m, NCH), 2.43-2.68 (1H, m, NCH), 2.11-2.25 (1H, m, HCH_2), 1.63-1.94 (3H, m, HCH_2). m/e (E.I.) 270, 269, 201. Exact mass (M^+) 270.1351 (Calcd. for $C_{16}H_{18}N_2O_2$ 270.1367).

Methyl (R)-[(S/RS)-2-(1-iodovinyl)pyrrolidin-1-yl]phenylacetate **(179a,b).**

Procedure (i):

To a solution of the allenic ester **(89)** (31.4mg, 0.13mmol) in THF (3ml) was added mercuric trifluoroacetate (56.3mg, 1.0eq) and the reaction stirred at room temperature for 30min.. Sodium carbonate (14.9mg, 1.1eq) was then added and the reaction stirred for a further 10 min.. Concentration *in vacuo*, addition of dichloromethane followed by filtration and concentration afforded the crude alkenylmercuric trifluoroacetate as a light yellow oil. This was dissolved in acetone (6ml), potassium iodide (189.2mg, 10.4eq) was added and the reaction stirred at room temperature under light-free conditions overnight. The reaction mixture was concentrated *in vacuo*, diluted in ether (10ml), washed with water (5ml) and brine (5ml), the organic layer dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude alkenylmercuric iodide as a colourless solid. This was dissolved in dichloromethane (3ml), cooled to -10°C, iodine (50.9mg, 0.2mmol) was added and the reaction stirred at room temperature under light-free conditions overnight. The reaction mixture was washed with saturated aqueous sodium sulphite solution (5ml), the organic layer dried ($MgSO_4$), concentrated *in vacuo* and then chromatographed on silica gel, eluting with dichloromethane/petrol (1:3) to afford the title compound as a colourless oil, (24.8mg, 53%).

Procedure (ii):

To a solution of the allenic ester **(89)** (30.0mg, 0.12mmol) in THF (3ml) was added sodium bicarbonate (29.9mg, 3.0eq) and iodine (163.3mg, 5.4 eq) and the reaction stirred at room temperature under light-free conditions for 2h. Saturated aqueous sodium thiosulphate (5ml) was added to the reaction mixture which was then extracted with ethyl acetate (10ml), the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel, eluting with petrol/ethyl acetate (7:1) afforded the title compound as a colourless oil (28.0mg, 62%).

(179a): $[\alpha]_D^{25}$ -70.5° (c 0.2, $CHCl_3$); υ_{max} ($CHCl_3$) 1725, 1600 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.27-7.40 (5H, m, ArH), 6.44 (1H, t, *J* 1 Hz, *cis*-HC=), 5.89 (1H, d, *J* 1 Hz, *trans*-HC=), 4.62 (1H, s, PhCH), 3.74 (3H, s, OCH_3), 3.08-3.16, 2.95-3.00, 2.72-2.80 (3H, 3 x m, NCH_2, HC-C=), 1.90-2.00 (1H, m, $\underline{H}CH_2$), 1.66-1.82 (3H, m,

HCH_2). **(179b)**: $[\alpha]_D^{25}$ +8.0° (c 0.2, $CHCl_3$); υ_{max} ($CHCl_3$) 1725, 1600 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.32-7.39 (5H, m, ArH), 6.32 (1H, t, *J* 1 Hz, *cis*-HC=), 5.78 (1H, d, *J* 1 Hz, *trans*-HC=), 4.52 (1H, s, PhCH), 3.67 (3H, s, OCH_3), 3.26-3.34, 2.94-2.97, 2.38-2.47 (3H, 3 x m, HC-C=, NCH_2), 1.60-1.92 (4H, m, 2 x CH_2). **(179a,b)**: m/e (C.I.) 372, 312 (E.I.) 312. Exact mass (M^+ -CO_2Me) 312.0251 (Calcd. for $C_{13}H_{15}NI$ 312.0250).

(R)-[(R/S)-2-(1-Iodovinyl)pyrrolidin-1-yl]-*N*-methylphenylacetamide **(180a,b).**

Procedure (i):

To a solution of the allenic amide **(90)** (39.5mg, 0.16mmol) in THF (3ml) was added sodium bicarbonate (49.6mg, 3.6eq) and iodine (205.3mg, 5.1eq). The reaction was stirred under light-free conditions at room temperature for 5h after which time it was diluted with saturated aqueous sodium thiosulphate (5ml) and ethyl acetate (5ml). The organic layer was separated, the aqueous layer extracted with ethyl acetate (2x5ml) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* followed by chromatography on silica gel, eluting with ethyl acetate/petrol (1:3) afforded the title compound as a colourless oil (19.8mg, 33%).

Procedure (ii):

To a solution of the alkenylmercuric chloride **(176)** (73.2mg, 0.15mmol) in acetone (6ml) was added potassium iodide (225.6mg, 9.1eq) and the reaction stirred under light-free conditions at room temperature overnight. The reaction mixture was concentrated *in vacuo*, diluted with water (5ml), extracted with ethyl acetate (10ml), the organic layer dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude alkenylmercuric iodide. This was dissolved in dichloromethane, (4ml), iodine (81.4mg, 2.1eq) was added and the reaction stirred under light-free conditions at room temperture overnight. After washing with saturated aqueous sodium sulphite solution, the organic phase was dried (Na_2SO_4); concentrated *in vacuo* and then chromatographed on silica gel, eluting with ethyl acetate/petrol

(1:3) to afford the title compound as a colourless oil (30mg, 53%). υ_{max} ($CHCl_3$) 3340, 1660, 1610 cm^{-1}; δ_H (270MHz, $CDCl_3$) **(180a)**: 7.57 (1H, br s, NH), 7.12-7.39 (5H, m, ArH), 6.46 (1H, s, *cis*-HC=), 5.98 (1H, s, *trans*-HC=), 4.37 (1H, s, PhCH), 2.88-2.96 (1H, m, HC-C=), 2.89 and 2.91 (3H, 2 x s, NCH_3), 2.49-2.54 (1H, m), 2.14-2.28 (1H, m, NCH), 1.56-1.93 (4H, m, 2 x CH_2). **(180b)**: 7.12-7.35 (5H, m, ArH), 7.02 (1H, br s, NH), 5.60 (1H, s, *cis*-HC=), 5.35 (1H, s, *trans*-HC=), 4.25 (1H, s, PhCH), 3.05-3.20 (1H, m, HC-C=), 2.91 and 2.92 (3H, 2 x s, NCH_3), 2.80-2.92 (2H, m, NCH_2), 1.63-1.92 (4H, m, 2 x CH_2). **(180a,b)**: m/e (C.I.) 371, 312, 243. Exact mass (MH^+) 371.063 (Calcd. for $C_{15}H_{20}N_2OI$ 371.062).

Methyl (R)-[(R/S)-2-(1-bromovinyl)pyrrolidin-1-yl]phenylacetate **(184a,b).**

Procedure (i):

To a solution of the allenic ester **(89)** (73.3mg, 0.3mmol) in carbon tetrachloride (5ml) was added *N*-bromosuccinimide (54.0mg, 1.0eq) and the reaction stirred under light-free conditions, at room temperature overnight. The reaction mixture was filtered, concentrated *in vacuo* and then chromatographed on silica gel, eluting with petrol/ether (25:1) to afford the title compound as a colourless oil (73.9mg, 77%).

Procedure (ii):

To a solution of the allenic ester **(89)** (32.4mg, 0.13 mmol) in carbon tetrachloride (4ml) was added sodium bicarbonate (60.6mg, 5.5 eq) followed by bromine in carbon tetrachloride until the orange colour was no longer discharged. The reaction was stirred at room temperature for a further 3.5h, then taken up in water (5ml) and dichloromethane (10ml). The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with petrol/ethyl acetate (15:1) to afford the product as a colourless oil (33.1mg, 77%). υ_{max} ($CHCl_3$) 1725, 1620 cm^{-1}; δ_H (270MHz, $CDCl_3$) **Mixture of diastereoisomers**: 7.29-7.36 (5H, m, ArH), 5.96 **(a)** and 5.82 **(b)** (1H, 2 x s, *cis*-HC=), 5.57 **(a)** and 5.43 **(b)** (1H, 2 x d, *J*

1.5 Hz, *trans*-HC=), 4.68 (**a**) and 4.59 (**b**) (1H, 2 x s, PhCH), 3.73 (**a**) and 3.67 (**b**) (3H, 2 x s, OCH_3), 3.60-3.78 (**a**) and 3.46-3.53 (**b**) (1H, 2 x m, HC-C=), 3.22-3.29 (**b**) and 3.03-3.11 (**a**) (1H, 2 x m, NCH), 2.73-2.82 (**a**) and 2.43-2.52 (**b**) (1H, 2 x m, NCH), 1.59-2.06 (4H, m, 2 x CH_2). m/e (C.I.) 326, 324, 266, 264 (E.I.) 266, 264. Exact mass (M^+ -CO_2Me) 264.0377 (Calcd. for $C_{13}H_{15}N\ ^{79}Br$ 264.0385).

Methyl (R)-phenyl{(R/S)-2-[1-(phenylseleno)vinyl]pyrrolidin-1-yl}acetate **(187a,b).**

To a solution of the ester (**89**) (59.1mg, 0.24 mmol) in dichloromethane (5ml) was added silica (60H, 90.0mg) and sodium carbonate (92.4mg, 3.6eq) and the mixture cooled to -78°C. A solution of phenylselenenyl chloride (60.0mg, 1.3eq) in dichloromethane (2ml) was added dropwise to the reaction mixture which was then stirred for 10 min. at -78°C, allowed to warm to room temperature and stirred under light-free conditions for 2 days. The reaction was quenched with water (5ml), extracted with dichloromethane (3x10ml), the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel, eluting with petrol/ether 40:1 afforded the title compounds as colourless oils; (**187a**) (52.1mg);(**187b**) (34.8mg) (combined yield 92%). (**187a**): $[\alpha]_D^{25}$ -79.8° (c 0.92, Et_2O); υ_{max} ($CHCl_3$) 1735, 1610, 1580 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.30-7.64 (10H, m, ArH), 5.67 (1H, s, *cis*-HC=), 4.85 (1H, s, *trans*-HC=), 4.76 (1H, s, PhCH), 3.68-3.73 (1H, m, HC-C=), 3.72 (3H, s, OCH_3), 3.09-3.20 and 2.68-2.79 (2H, 2 x m, NCH_2), 1.95-2.19 and 1.72-1.92 (4H, 2 x m, 2xCH_2); δ_C (68MHz $CDCl_3$) 136.26 (d), 135.71 (s), 129.38 (s), 129.22 (d), 128.60 (d), 128.31 (d), 128.02 (d), 127.66 (d), 126.56 (s), 113.13 (t), 67.76 (d), 64.48 (d), 51.21 (q), 47.26 (t), 33.15 (t), 23.48 (t) (Carbonyl C not observed). (**187b**): $[\alpha]_D^{25}$ -47.1 (c 0.63, Et_2O); υ_{max} ($CHCl_3$) 1735, 1610, 1580 cm^{-1}; δ_H (270MHz, $CDCl_3$) 7.25-7.63 (10H, m, ArH), 5.66 (1H, s, *cis*-HC=), 4.82 (1H, s, *trans*-HC=), 4.67 (1H, s, PhCH), 3.70 (3H, s, OCH_3), 3.31-3.46 (2H, m, HC-C=, NCH), 2.23-2.40 (1H, m, NCH), 1.82-2.00 and 1.57-1.68 (4H, 2 x m, 2xCH_2); δ_C (68MHz $CDCl_3$) 136.16

(d), 135.13 (s), 130.91 (s), 129.74 (d), 129.61 (d), 129.19 (d), 128.18 (d), 127.92 (d), 126.66 (s), 113.43 (t), 66.78 (d), 66.52 (d), 51.70 (q), 48.94 (t), 31.98 (t), 23.03 (t) (Carbonyl C not observed). **(187a,b)**: m/e (E.I.) 401, 399, 342, 340, 218. Exact mass (M^+) 401.0891. (Calcd. for $C_{21}H_{23}NO_2{}^{80}Se$ 401.0891).

N-[(S)-α-Methylbenzyl]-(S)-2-[1-(hydroxymethyl)vinyl]pyrrolidine **(188)** and *N*-[(S)-α-Methylbenzyl]-(R)-2-[1-(hydroxymethyl)vinyl]pyrrolidine *epi*-**(188)**

To a solution of the ester **(144a,b)** (9.6g, 37 mmol) in THF (200 ml) was added a solution of DiBAl in toluene (1.5M, 50 ml, 2.0 eq) dropwise at -78°C and the reaction mixture allowed to warm to room temperature over 30 min.. Saturated aqueous ammonium chloride was added and the resulting slurry filtered through a pad of Celite, washing with dichloromethane, to afford, on concentration, the title compound as a light yellow oil (8.35g, 98%). This was used in the next step without further purification. **(188)**: $[\alpha]_D{}^{19}$ -44.0° (c 0.28, $CHCl_3$); υ_{max} (film) 3400, 1640, 1600, 1500 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.22-7.37 (5H, m, ArH), 5.07 (1H, s, HC=), 5.01 (1H, d, *J* 2 Hz, HC=), 4.58 (1H, dd, *J* 12, 0.5 Hz, OCH), 4.17 (1H, d, *J* 12 Hz, OCH), 3.92 (1H, q, *J* 7 Hz, PhCH), 3.35-3.40 (1H, m, NCH), 2.93-2.99 (1H, m, HC-C=), 2.18-2.31 (1H, m, NCH), 1.76-1.94 (3H, m, HCH_2), 1.60-1.73 (1H, m, $\underline{H}CH_2$), 1.48 (3H, d, *J* 7 Hz, CH_3), 1.26 (1H, s, OH); δ_C (68 MHz, $CDCl_3$) 147.71 (s), 140.44 (s), 128.31 (d), 128.09 (d), 127.18 (d), 114.01 (t), 66.62 (d), 65.49 (t), 60.07 (d), 48.85 (t), 30.42 (t), 23.77 (t), 21.24 (q). *epi*-**(188)**: $[\alpha]_D{}^{19}$ +7.7° (c 2.1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 7.16-7.37 (5H, m, ArH), 4.88 (1H, s, HC=), 4.78 (1H, d, *J* 2 Hz, HC=), 4.48 (1H, d, *J* 12.5 Hz, OCH), 4.09 (1H, d, *J* 12.5 Hz, OCH), 4.03 (1H, q, *J* 7 Hz, PhCH), 3.51-3.57 (1H, m, NCH), 2.79-2.83 (1H, m, HC=C=), 2.48-2.57 (1H, m, NCH), 1.73-2.06 (5H, m, 2 x CH_2, OH), 1.37 (3H, d, *J* 7 Hz, CH_3); δ_C (68 MHz, $CDCl_3$) 147.22 (s), 128.35 (s), 128.15 (d), 127.96 (d), 126.95 (d), 113.68 (t), 66.65 (d), 65.26 (t), 57.77 (d), 47.35 (d), 30.13 (t), 23.87 (t), 12.91 (q). **(188)**/*epi*-**(188)**: m/e (E.I.) 231, 216, 174. Exact mass (M^+) 231.1633 (Calcd. for $C_{15}H_{21}NO$ 231.1623).

(R/S)-8-Hydroxy-8-methyl-6(Z)-propylidene-(8a R/S)-octahydro-5-indolizidinone Z-(**195**) and (R/S)-8-Hydroxy-8-methyl-6(Z)-propylidene-(8a R/S)-octahydro-5-indolizidinone E-(**195**).

Procedure (i):

To a solution of the hydroxylactam (**75a**) (104.8mg, 0.62 mmol) in THF (5ml) was added LDA in THF (0.64M, 1.9ml, 1.97 eq) at -78°C. The reaction was warmed to 0°C, stirred for 30 min. and pentanal (0.07ml, 1.0 eq) in THF (1ml) was added to the reaction mixture at -78°C. The reaction was stirred at -78°C for 30min., quenched with water (2ml), extracted with ether (2x), dried (Na_2SO_4) and evaporated *in vacuo* to afford a colourless oil. This was dissolved in pyridine (3ml) and to the solution was added methanesulphonyl chloride (0.05ml, 1.0 eq) at 0°C. The reaction was stirred at room temperature for 30 min., concentrated *in vacuo* and then dissolved in methanol (5 ml). Powdered potassium hydroxide (350mg) was added, the reaction stirred at room temperature for 12h., then diluted with water (5ml) and extracted with dichloromethane (3x). The combined organic layers were dried (Na_2SO_4), evaporated *in vacuo* and chromatographed on silica, eluting with 80% ethyl acetate/petrol, to afford Z-(**195**) (17.1mg) and Z-(**195**) (24.5mg) as colourless solids, combined yield 29%.

Procedure (ii):

To a solution of the hydroxylactam (**75a**) (97.1 mg, 0.57 mmol) in THF (12ml) was added a solution of LDA in THF (0.44M, 2.62ml, 2 eq) at -78° and the reaction stirred for 30 min.. Pentanal (0.07ml, 1.1 eq) in THF (1ml) was added to the reaction mixture at -78°C which was stirred for 30 min. then allowed to warm to 0°C over 30 min.. The reaction was quenched with saturated aqueous ammonium chloride solution (2ml), extracted with ethyl acetate (2x), dried (Na_2SO_4) and evaporated to afford a mixture of aldol products (75.4mg).

To a solution of the aldol mixture (30.4mg, 0.12 mmol) in toluene (3ml) was added copper(I) chloride (5mg, 0.42 eq) and DCC (29.0mg, 1.2 eq) and the reaction

heated to reflux for 7h. Concentration *in vacuo*, dilution with dichloromethane, filtration and washing the solution with dilute aqueous ammonia, was followed by drying of the organic layer (Na_2SO_4) and evaporation *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate/petrol (3:1) afforded Z-(**195**) (9.6 mg) and E-(**195**) (7.2 mg) as colourless solids, combined yield 59%.

Procedure (iii):

To a solution of the enelactam E-(**197**) (28.4mg, 0.13 eq) in THF/water (2:3, 5ml) was added mercuric acetate (29.2mg, 0.7 eq) and the reaction stirred at room temeperature for 2h. Sodium borohydride (10.0mg, 2 eq) in aqueous sodium hydroxide solution (2M, 1ml) was added, the reaction stirred for 5 min., extracted with dichloromethane (3x), filtered through Celite and concentrated *in vacuo*. Chromatography on silica gel afford E-(**195**) as a colourless solid (22.6 mg) in a yield of 89%, based on recovered E-(**197**) (5.0mg). Z-(**195**): υ_{max} ($CHCl_3$) 3400, 1655, 1595 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.89 (1H, td, *J* 6.5, 2 Hz, HC=), 3.53-3.58 (2H, m, NCH_2), 3.46 (1H, dd, *J* 10, 3.5 Hz, NCH), 2.75-2.89 (2H, m, $COC{=}C\text{-}CH_2$), 2.69 (1H, dq, *J* 15, 2.5 Hz, HβC-C=), 2.47 (1H, d, *J* 15, HαC-C=), 1.71-2.03 (5H, m, 2 x ring CH_2, OH), 1.31-1.47 (4H, m, 2 x CH_2), 1.28 (3H, s, CH_3), 0.90 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$); δ_C (68 MHz, $CDCl_3$) 163.96 (s), 146.44 (d), 124.19 (s), 67.69 (s), 66.62 (d), 47.90 (t), 45.51 (t), 31.92 (t), 29.13 (t), 26.14 (t), 25.20 (q), 22.54 (t), 22.18 (t), 13.98 (q). m/e (E.I.) 237, 194. Exact mass (M^+) 237.1729 (Calcd. for $C_{14}H_{23}NO_2$ 237.1728). E-(**195**): υ_{max} ($CHCl_3$) 3380, 1655, 1595 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.96 (1H, td, *J* 7.5, 1.5 Hz, HC=), 3.48-3.70 (3H, m, NCH_2, NCH), 2.75 (1H, d, *J* 16.5 Hz, HαC-C=), 2.36 (1H, ddt, *J* 16.5, 3, 1.5 Hz, HβC-C=), 1.67-2.21 (7H, m, $COC{=}C\text{-}CH_2$, 2 x ring CH_2, OH), 1.25-1.50 (4H, m, 2 x CH_2), 1.31 (3H, s, CH_3), 0.90 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$); δ_C (68 MHz, $CDCl_3$), 141.52 (d), 67.79 (s), 65.78 (d), 46.19 (t), 39.60 (t), 30.72 (t), 27.96 (t), 26.44 (t), 25.40 (q), 22.51 (t), 22.32 (t), 13.88 (q),(Carbonyl C and olefin C singlets not observed); m/e (E.I.) 237, 194; Found: C, 70.8; H, 10.0; N,5.8%.(Calcd. for $C_{14}H_{23}NO_2$; C, 70.9; H, 9.7; N, 5.9%).

6-[1-Hydroxypropyl]-8-methylene-(8a R/S)-octahydro-5-indolizidinone (**196a-d**).

To a solution of LDA in THF (0.11M, 5ml, 0.55 mmol) was added a solution of the lactam (**77**/*ent*-**77**) (72.5mg, 0.48 mmol) in THF (1.5ml) at -78°C. The reaction was warmed to 0°C, stirred for 30 min. and a solution of pentanal (0.08ml, 1.5 eq) in THF (1.5ml) was then added at -78°C. The reaction was stirred for 20 min. then warmed to room temperature over 15 min., quenched with saturated aqueous ammonium chloride solution (2ml) and extracted with ethyl acetate (2x). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford a residue which yielded, on silica gel chromatography eluting with ethyl acetate/petrol (4:1), (**196a,b,c**) as a mixture of aldols (31.0mg) and (**196d**) as a single diastereoisomer (24.8mg) in a combined yield of 68% based on recovered lactam (**77**/*ent*-**77**) (20.3mg). (**196a-c**): υ_{max} ($CHCl_3$) 3400, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.98-5.04 (1H, m, HC=), 4.94 (1H, br s, HC=), 3.43-4.20 (5H, m, HC-C=, HCOH, NCH_2), 1.63-2.64 (7H, m, H_2C-C=, COCH, 2 x ring CH_2), 1.27-1.62 (6H, m, 3 x CH_2), 0.88-0.95 (3H, m, CH_3); (**196d**): υ_{max} ($CHCl_3$) 3400, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.98 and 4.92 (2H, 2 x s, H_2C=), 3.93-4.14 (2H, m, OCH, HC-C=), 3.64 (1H, ddd, *J* 12, 10, 8 Hz, NCH), 3.47 (1H, ddd, *J* 10, 9, 2 Hz, NCH), 2.88 (1H, br s, OH), 2.41-2.57 (3H, m, H_2C-C=, COCH), 1.63-2.21 (4H, m, 2 x ring CH_2), 1.24-1.61 (6H, m, 3 x CH_2), 0.91 (3H, t, *J* 7 Hz, CH_3); δ_C (68 MHz, $CDCl_3$) 170.84 (s), 142.39 (s), 109.31 (t), 71.62 (d), 61.20 (d), 48.23 (d), 44.99 (t), 32.89 (t), 31.17 (t), 29.94 (t), 28.48 (t). 22.67 (t), 22.06 (t), 14.01 (q). (**196a-d**): m/e (E.I.) 237, 180, 150. Exact mass (M^+) 237.1734 (Calcd. for $C_{14}H_{23}NO_2$ 237.1729).

8-Methylene-6(Z)-propylidene-(8a R/S)-octahydro-5-indolizidinone Z-(**197**) and 8-Methylene-6(Z)-propylidene-(8a R/S)-octahydro-5-indolizidinone E-(**197**).

Procedure (i)

To a solution of the aldol mixture (**196a-d**) (47.1mg, 0.20 mmol) in pyridine (2ml) was added methanesulphonyl chloride (0.04ml, 3 eq) at 0°C and the reaction

stirred for 10 min.. Concentration *in vacuo* followed by dilution with methanol (3ml), additon of powdered potassium hydroxide (120mg, 10.7 eq) and stirring overnight effected elimination. After 12h, addition of water (5ml) extraction with dichloromethane (3x) drying (Na_2SO_4), concentration *in vacuo* and chromatography on silica gel, eluting with ethyl acetate/petrol (3:1) afforded Z-(**197**) (11.8mg) and E-(**197**) (28.4 mg) as colourless oils, combined yield 92%.

Procedure (b)

To a solution of the aldol mixture (**196a-d**) (40.0mg, 0.17 mmol) in toluene (4ml) was added copper(I) chloride (5mg, 0.3 eq) and DCC (42.0mg, 1.2 eq) and the reaction heated to reflux for 15h. Dilution with dilute aqueous ammonia (10ml) and extraction with ethyl acetate (3x), drying (Na_2SO_4) and concentation *in vacuo* afforded, on silica gel chromatography eluting with ethyl acetate/petrol (4:1), Z-(**197**) (10.5mg) and E-(**197**) (15.0mg) as colourless oils, combined yield 69%.

Z-(**197**): υ_{max} ($CHCl_3$) 1650, 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$). 5.75 (1H, tt, *J* 7.5, 1.5 Hz, CO-C=CH), 4.93 and 4.87 (2H, 2 x t, *J* 1 Hz, HC=); 3.99-4.04 (1H, m, NCH-C=), 3.65 (1H, ddd, *J* 12.5, 9.5, 8 Hz, NCH), 3.52 (1H, ddd, *J* 14, 8, 2 Hz, NCH), 3.21 (1H, dp, *J* 16, 1.5 Hz, HC-C=), 3.11 (1H, dp, *J* 16, 1 Hz, HC-C=), 2.61-2.69 (2H, m, H_2C-C=), 1.66-2.20 (4H, m, 2 x ring CH_2), 1.30-1.46 (4H, m, 2 x CH_2), 0.90 (3H, t, *J* 7 Hz, CH_3); δ_C (68 MHz, $CDCl_3$) 143.01 (s), 140.54 (d), 127.63 (s), 108.17 (t), 61.08 (d), 44.50 (t), 40.19 (t), 31.92 (t), 30.68 (t), 28.74 (t), 22.54 (t), 22.48 (t), 13.98 (q), (Carbonyl C not observed); m/e (E.I.) 219, 190. Exact mass (M^+) 219.1607 (Calcd. for $C_{14}H_{21}NO$ 219.1622).

E-(**197**): υ_{max} ($CHCl_3$) 1655, 1590 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.79 (1H, tq, *J* 6, 1.5 Hz, COC=CH), 4.97 and 4.91 (2H, 2 x br s, H_2C=), 4.01-4.07 (1H, m, NCH-C=), 3.55-3.65 (2H, m, NCH_2), 3.32 and 3.08 (2H, 2 x d, *J* 17 Hz, H_2C-C=), 1.71-2.20 (6H, m, $COCH_2$, 2 x ring CH_2), 1.25-1.50 (4H, m, 2 x CH_2), 0.91 (3H, t, *J* 7 Hz, CH_3); δ_C (68 MHz, $CDCl_3$) 163.99 (s), 141.61 (s), 137.65 (d), 127.99 (s), 108.79 (t), 60.62 (d), 45.41 (t), 33.76 (t), 30.68 (t), 29.94 (t), 29.32 (t), 27.79 (t), 22.44 (t), 13.85 (q). m/e (E.I.) 219, 190, 162. Exact mass (M^+) 219.1619 (Calcd.

for $C_{14}H_{21}NO$ 219.1622).

(R/S)-8-Methyl-8-(trimethylsilyloxy)-(8a R/S)-octahydro-5-indolizidinone (**199**).

To a solution of the hydroxylactam (**75a**) (45.0mg, 0.28 mmol) in THF (4ml) was added a solution of LDA in THF (1.1M, 0.54ml, 2.2 eq) at -78°C. The reaction was stirred at -78°C for 40 min. and this was followed by the rapid addition of trimethylsilyl chloride (0.14ml, 4 eq) and warming of the reaction mixture to room temperature over 30 min.. The reaction was quenched with saturated aqueous ammonium chloride solution (1ml), extracted with dichloromethane (3x), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate, afforded the title compound as a colourless oil (44.7 mg, 70%); υ_{max} 1610 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 3.42-3.48 (2H, m, NCH_2), 3.19 (1H, dd, *J* 8.5, 5.5 Hz, NCH), 2.24-2.49 (2H, m, $COCH_2$), 1.60-1.91 (6H, m, 3 x CH_2), 1.27 (3H, s, CH_3), 0.07 (9H, s, $OSi(CH_3)_3$). m/e (E.I.) 241, 198, 143, 111, 83. Exact mass (M^+) 241.1488 (Calcd. for $C_{12}H_{23}NO_2Si$ 241.1496).

8-Methylene-6-trimethylsilyl-(R/S)-octahydro-5-indolizidinone (**200**).

To a solution of the lactam (**77**/*ent***77**) (135mg, 0.89 mmol) in THF (5ml) was added a solution of LDA in THF (1.1M, 0.95ml, 1.2 eq) at -78°C. The reaction was stirred for 40 min. after which time trimethylsilyl chloride (0.23ml, 2 eq) was rapidly added and the reaction mixture warmed to room temperature over 15 min.. Quenching with saturated aqueous ammonium chloride solution (1ml), extraction with dichloromethane (2x), drying (Na_2SO_4) and concentration *in vacuo* was followed by chromatography in silica gel, eluting with ethyl acetate/petrol (1:9), to afford the title compound as a colourless oil (31.1mg) in a yield of 28% based on recovered (**77**/*ent***77**) (61.0mg). υ_{max} ($CHCl_3$) 1600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.82 (1H, p, *J* 1 Hz, HC=), 4.76 (1H, q, *J* 1 Hz, HC=), 3.80 (1H, dd, *J* 5, 11 Hz, HC-C=), 3.58 (1H, ddd, *J* 11, 10, 9 Hz, NCH), 3.27 (1H, ddd, *J* 13, 9, 2 Hz, NCH), 2.41 (1H, ddd, *J* 14.5, 7, 1 Hz, HC-C=), 2.25 (1H, dd, *J* 14.5, 7.5 Hz, HC-C=),

1.46-2.03 (5H, m, 2 x CH_2, COCH), 0.00 (9H, s, $Si(CH_3)_3$). Further analysis was precluded by rapid desilylation of **(200)**.

O-Acetyl-6-[1-hydroxypropyl]-8-methylene-5-indolizidinone **(201)**.

To a solution of the aldol **(196d)** (20.0mg, 0.084 mmol) in pyridine (1ml) was added acetic anhydride (0.5ml) and 4-*N,N*-dimethylaminopyridine (1mg) at 0°C. The reaction was stirred for 30 min., diluted with dilute aqueous hydrochloric acid (5ml), extracted with ethyl acetate (2x), the organic layer washed with saturated aqueous sodium bicarbonate solution (5ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by chromatography eluting with ethyl acetate/petrol (1:3), afforded the title compound as a colourless oil (15.8mg, 67%). υ_{max} ($CHCl_3$) 1730, 1620 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.40 (1H, ddd, *J* 7, 6, 5.5 Hz, HC-OAc), 4.98 and 4.94 (2H, 2 x s, H_2C=), 4.02 (1H, dd, *J* 11, 5.5 Hz, HC-C=), 3.66 (1H, dt, *J* 12, 8 Hz, NCH), 3.44 (1H, ddd, *J* 12, 10, 2 Hz, NCH), 2.49-2.62 (2H, m, H_2C-C=), 2.17 (1H, dt, *J* 11, 5.5 Hz, COCH), 1.53-2.06 (6H, m, 2 x ring CH_2, H_2C-COAc), 2.03 (3H, s, $COCH_3$), 1.20-1.38 (4H, m, 2 x CH_2), 0.89 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$); δ_C (68 MHz, $CDCl_3$) 170.06 (s), 110.02 (t), 72.91 (d), 60.91 (d), 46.22 (d), 45.12 (t), 31.85 (t), 31.01 (t), 30.65 (t), 27.54 (t), 22.54 (t), 22.15 (t), 21.08 (q), 13.95 (q). Ester carbonyl C and olefin C singlets not observed. m/e (E.I.) 279, 219, 150. Exact mass (M^+) 279.1844 (Calcd. for $C_{16}H_{25}NO_3$ 279.1833).

N-Hexanoyl-(R)-4-methyl-(S)-5-phenyl-2-oxazolidinone **(206)**.

To a solution of (4R, 5S)-4-Methyl-5-phenyl-2-oxazolidinone (1.42g, 8.0 mmol) in THF (50ml) was added *n*BuLi in THF (1.6M, 6.7ml, 1.3 eq) at -78°C and the reaction stirred for 30 min.. This was followed by addition of a solution of hexanoyl chloride (1.67ml, 1.5 eq) in THF (10ml) at -78°C and warming to room temperature over 30 min.. Quenching the reaction with saturated aqueous ammonium chloride (10ml), extraction with ether (2x30ml), drying ($MgSO_4$) and evaporation afforded a solid residue. Recrystallisation from petrol afforded the

title compound as a colourless solid (1.99g, 91%). m.p. 60-61°C; $[\alpha]_D^{19}$ +142°, (c 1.47, $CHCl_3$); υ_{max} ($CHCl_3$) 1750 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.27-7.46 (5H, m, ArH), 5.67 (1H, d, *J* 7 Hz, PhCH), 4.77 (1H, p, *J* 7 Hz, MeCH), 2.83-3.06 (2H, m, $COCH_2$), 1.63-1.74 (2H, m, COC-CH_2), 1.32-1.43 (4H, m, 2 x CH_2), 0.88-0.94 (6H, m, 2 x CH_3). m/e (E.I.) 275, 237, 219. Exact mass (M^+) 275.1515 (Calcd. for $C_{16}H_{21}NO_3$ 275.1521).

(R)-4-Methyl-*N*-[(R)-2-methylhexanoyl]-(S)-5-phenyl-2-oxazolidinone (**207**).

To a solution of LDA in THF (0.15M, 50ml, 7.5 mmol) at -78°C was added a solution of (**206**) (1.91g, 6.9 mmol) in THF (10ml) and the reaction warmed to -20°C over 40 min.. This was followed by addition of methyl iodide (1.30ml, 3 eq) in THF (2ml) at -40°C, warming to 0°C and stirring for 1h at 0°C. The reaction was quenched with water (40ml), extracted with ether (2x50ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on flash silica, eluting with ether/petrol (1:4) afforded the title compound as a colourless oil (1.18 g, 59%). $[\alpha]_D^{19}$ +11.9° (c 0.69, $CHCl_3$); υ_{max} ($CHCl_3$) 1770, 1680 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.30-7.48 (5H, m, ArH), 5.67 (1H, d, *J* 7 Hz, PhCH), 4.79 (1H, p, *J* 7 Hz, MeCH), 3.67-3.79 (1H, m, COCH), 1.68-1.82 (1H, m, COC-CH), 1.25-1.51 (4H, m, 2 x CH_2), 1.19 (3H, d, *J* Hz, COC-CH_3), 0.87-0.96 (6H, m, 2 x CH_3). m/e (E.I.) 289, 233, 176. Exact mass (M^+) 289.1654 (Calcd. for $C_{17}H_{23}NO_3$ 289.1676).

(R)-2-Methylhexanol (**208**).

To a solution of lithium aluminium hydride (0.50 g, 13 mmol) in THF (50ml) was added a solution of (**207**) (1.18 g, 4.1 mmol) in THF (10ml) at 0°C with rapid stirring. After 1h., the reaction was quenched with saturated aqueous sodium sulphate solution and filtered through Celite, washing with dichloromethane. Concnetration i*n vacuo* followed by chromatography on flash silica, eluting with ether/petrol (1:3), afforded the title compound as a colourless oil (357 mg, 75%). $[\alpha]_D^{18}$ +8.1° (c 0.67, Et_2O); +9.5° (c 14.2, Et_2O); υ_{max} (film) 3300 cm^{-1}; δ_H (270

MHz, $CDCl_3$) 3.51 and 3.41 (2 x dd, *J* 10.5, 6 Hz, OCH_2), 1.55-1.67 (1H, m, MeCH), 1.45 (1H, s, OH), 1.06-1.44 (6H, m, 3 x CH_2), 0.92 (3H, d, *J* 6.5 Hz, $C\underline{H}_3CH$), 0.84-0.92 (3H, m, $C\underline{H}_3CH_2$).

(S)-8-Hydroxy-6-[1-hydroxy-(R)-2-methylhexyl]-8-methyl-(8a S)-octahydro-5-indolizidinone (**209a-c**).

A solution of the hydroxylactam (**75a,b**) (10:1 mixture, 75.8mg, 0.45 mmol) in THF (2ml) was added to a solution of LDA in THF (0.094M, 10ml, 2.1 eq) at -78°C. The reaction was stirred at -78°C for 30 min. and to the resultant dianion was added a solution of the aldehyde (**76**) derived from alcohol (**207**) (58.2mg, 1.1 eq) as described above and the reaction mixture warmed to 0°C over 30 min.. The reaction was quenched with saturated aqueous ammonium chloride solution (1ml), extracted with ethyl acetate (3x30ml), dried (Na_2SO_4), concentrated *in vacuo* and chromatographed on silica gel, eluting with ethyl acetate/petrol (1:4). Three aldol components were isolated; (**209a,b**) a mixture of two aldol isomers as a colourless oil, (41.5mg) and (**209c**), a single aldol isomer, as a colourless solid (25.8mg)in a combined yield of 69% based on recovered (**75a,b**) (17.5mg). (**209c**) was further purified by recrystallisation from ether/petrol to afford colourless crystals. (**209c**): m.p. 151-152°C; $[\alpha]_D^{21}$ -7.8 (c 1.2, $CHCl_3$); υ_{max} ($CHCl_3$) 3400, 1610 cm^{-1}; δ_H (270 m MHz, $CDCl_3$) 4.03 (1H, dd, *J* 8.5, 2.5 Hz, $\underline{H}COH$), 3.51-3.56 (2H, m, N-CH_2), 3.39-3.45 (1H, m, NCH), 2.80 (1H, ddd, *J* 11.5, 7.5, 3 Hz, COCH), 1.74-1.99 (8H, m, 3 x ring CH_2, 2 x OH), 1.47-1.56 (1H, m, MeCH), 1.32 (3H, s, CH_3), 1.09-1.37 (6H, m, 3 x CH_2), 0.97 (3H, d, *J* 6.5 Hz, $CHC\underline{H}_3$), 0.90 (3H, t, *J* 6.5 Hz, $CH_2C\underline{H}_3$); δ_C (68 MHz, $CDCl_3$) 75.44 (d), 68.08 (s), 65.78 (d), 46.12 (t), 41.52 (d), 35.26 (d), 34.96 (t), 32.63 (t), 28.90 (t), 26.56 (q), 26.24 (t), 22.96 (t), 22.06 (t), 15.47 (q), 14.11 (q), (Carbonyl C not observed).

Overlapping signals for (**209a,b**) complicated proton NMR analysis. (**209c**): m/e (C.I.) 284 (E.I.) 265, 226, 198, 169, 70. Exact mass (M^+-H_2O) 265.2054 (Calcd. for $C_{16}H_{27}NO_2$ 265.2042).

(+)-Tashiromine (**212**).

To a solution of *ent*-(**77**) (80.0mg, 0.53 mmol) in THF (15ml) was added a solution of borane-dimethylsulphide complex in THF (2M, 0.29ml, 1.1 eq) and the reaction stirred at room temperature for 30 min.. Absolute ethanol (1ml) followed by aqueous sodium hydroxide (2M, 3ml) and aqueous hydrogen peroxide (30%, 0.2ml, 3.7 eq) were then added to the reaction mixture which was subsequently heated to reflux for 3h. Extraction with ethyl acetate (3x), drying (Na_2SO_4) and evaporation *in vacuo* afforded a residue which was dissolved in DMSO (2ml). To this solution was added triethylamine (0.44ml, 6.0 eq) and pyridine-sulphur trioxide complex (212mg, 2.6 eq) and the reaction stirred at room temperature for 30 min..

Dilution with water, followed by extraction with ether/30-40 petrol, (1:1) (3x), washing the combined organic layers with brine (3x) afforded on drying ($MgSO_4$) and concentration *in vacuo* the crude aldehyde mixture. This was dissolved in methanol (8ml) and sodium methoxide (29mg, 1.0 eq) was added, the reaction stirred for 30 min., diluted with ($MgSO_4$) and concentrated in vacuo. The resulting oil was dissolved in ether (5ml) and a solution of lithium aluminium hydride in ether (1M, 0.5ml, 0.94 eq) was added at room temperature. The reaction was stirred for 10 min., quenched with saturated aqueous sodium sulphate solution, filtered, evaporated *in vacuo* and chromatographed on silica gel, eluting with dichloromethane/methanol/ammonia (90:10:1) to afford the title compound as a colourless oil, (5.4mg, 6.6%).

$[\alpha]_D^{20}$ +12.8° (c 0.54, EtOH); υ_{max} ($CHCl_3$) 3620, 3380, 1440 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 3.66 (1H, dd, *J* 10.5, 4.5 Hz, OCH), 3.47 (1H, dd, *J* 10.5, 6 Hz, OCH), 3.18-3.25 (2H, m, NCH_2), 1.56-2.27 (13H, m, OH, NCH, OC-CH, 5 x CH_2); δ_C (68 MHz, $CDCl_3$) 66.4, 65.9, 54.2, 52.7, 44.7, 29.2, 27.6, 25.2, 20.3. m/e (E.I.) 155, 154, 138, 124, 97, 96, 84, 69. Exact mass (M^+) 155.1310 (Calcd. for $C_9H_{17}NO$ 155.1310).

REFERENCES

1 a)Daly, J.W. and Myers, C.W. *Science*, 156, 970 (1967).

b)Daly, J.W. *Prog. Chem. Org. Nat. Prod.*, 41, 205 (1982).

c)Witkop, B and Gossinger, E. in *The Alkaloids*, Brossi, A., Ed.; Academic Press, New York, Vol. 21 (1983), Chapter 5.

d)Myers, C.W. and Daly, J.W. *Scientific American*, 248 (2), 97 (1983).

2 Cochrane, C.S. *Journal of a residence and travels in Columbia during the years 1823 and 1824*; Henry Colburn, London (1925).

3 a)Tokuyama, T, and Daly, J.W. *Tetrahedron*, 39, 41 (1983).

b)Daly, J.W.; Spande, T.F.; Whittaker, N.; Highet, R.J.; Feigh, D.; Nishimori, N.Tokuyama, T. and Meyers, G.W. *J. Nat. Prod.*, 49, 265 (1986).

c)Tokuyama, T.; Nishimori, N.; Karle, I.L.; Edwards, M.W and Daly, J.W. *Tetrahedron*, 42, 3453 (1986).

d)Tokuyama, T.; Nishimori, N.; Shimada, A; Edwards, M.W. and Daly , J.W. *Ibid.*, 43, 643 (1987).

4 a)Overman, L.E. and Bell, K.L. *J. Am. Chem. Soc.*, 103, 1851 (1981).

b)Overman, L.E. and McCready, R.J. *Tetrahedron Lett.*, 23, 2355 (1982).

c)Overman, L.E. and Goldstein, S.W. *J. Am. Chem. Soc.*, 106, 5360 (1984).

d)Overman, L.E.; Bell, K.L. and Ito, F. *Ibid.*, 106, 4192 (1984).

e)Overman, L.E. and Lin, N.-H., *J. Org. Chem.*, 50, 3669 (1985).

f)Overman, L.E and Sharp, M.J. *Tetrahedron Lett.*, 29, 901 (1988).

g)Lett, R.M.; Overman, L.E. and Zablocki, J. *Ibid.*, 29, 6541 (1988).

h)Trost, B.M. and Scanlan, T.S. *J. Am. Chem. Soc.*, 111, 4988 (1989).

i)Smith, A.L.; Williams, S.F.; Holmes, A.B.; Hughes, L.R.; Lidert, Z. and Swithenbank, C. *Ibid.*, 110, 8696 (1988).

j)Iida, H.; Watanabe, Y. and Kibayashi, C. *Ibid.*, 107, 5534 (1985).

k)Broka, C.A. and Eng, K.K. *J. Org. Chem.*, 51, 5043 (1986).

5 Märki, F. and Witkop, B. *Experimentia*, 19, 329 (1963).

6 a)Daly, J.W.; Brown, G.B.; Mensah-Dwumah, M. and Myers, C.W. *Toxicon*, 16, 163 (1978).

b)Highet, R.J.; Daly, J.W.; Fujiwara, T. and Tokuyama, T. *Planta Medica*, 39, 260 (1980).

c)Albuquerque, E.X.; Warnick, J.E.; Maleque, M.A.; Kauffman, F.C.; Tamburini, R; Nimit, Y and Daly, J.W. *Mol. Pharmacol.*, 19, 411 (1981)

d)Tamburini, R.; Albuquerque, E.X.; Daly, J.W. and Kauffman, F.C. *J. Neurochem.*, 37, 775 (1981).

e)Daly, J.W.; McNeal, E.T.; Overman, L.E. and Ellison, D.H. *J. Med. Chem.*, 28, 482 (1985).

f)Rao, K.S.; Warnick, J.E.; Daly, J.W. and Albuquerque, E.X. *J. Pharmacol. Exp. Ther.*, 243, 775 (1987).

g)Daly, J.W.; McNeal, E.; Gusovsky, F.; Ito, F. and Overman, L.E. *J. Med. Chem.*, 31, 477 (1988).

h)Gusovsky, F.; Rossignol, D.P.; McNeal, E.T. and Daly, J.W. *Proc. Natl. Acad. Sci. USA*, 85, 1272 (1988).

i) Daly, J.W.; Gusovsky, F.; McNeal, E.T.; Secunda, S.; Bell, M.; Creveling, C.R.; Nishizawa, Y.; Overman, L.E.; Sharp, M.J. and Rossignol, D.P. *Biochemical Pharmaoclogy*, 40, 315 (1990).

7 a)Azzouzi, A.; Dufour, M.; Gramain, J.-C. and Remuson, R. *Heterocycles*, 27, 133 (1988).

b)Overman, L.E. and Lesuisse, D. *Tetrahedron Lett.*, 26 4167 (1985).

8 a)Schultz, A.G.; McCloskey, P.J. and Court, J.J. *J. Am. Chem. Soc.*, 109, 6493

(1987).

b)Inubushi, Y. and Ibuka, T. *Heterocycles*, 8, 633 (1977).

c)Grieco, P.A. and Parker, D.T. *J. Org. Chem.*, 53, 3658 (1988)

9 Daly, J.W.; Tokuyama, T.; Fujiwara, T; Highet, R.J. and Karle, I.L. *J. Am. Chem. Soc.*, 102, 830 (1980).

10 a)Tokuyama, T.; Shimada, K. and Uemura, M.*Tetrahedron Lett.*, 23, 2121 (1982).

b)Tokuyama, T.; Daly, J.W. and Highet, R.J. *Tetrahedron*, 40, 1183 (1984).

11 Gusovsky, F.; McNeal, E.T. and Daly, J.W. *Mol. Pharmacol.*, 32, 479 (1987).

12 Catterall, W.A. *J. Biol. Chem.*, 252, 8669 (1977).

13 Abdel-Latif, A.A. *Pharmacol. Dev.*, 38, 227 (1986).

14 Midland, M.M..; McDowell, D.C.; Hatch, R.L. and Tramontano, A. *J. Am. Chem. Soc.*, 102, 867 (1980).

15 For reviews in this area see: Cardillo, G. and Orena, M. *Tetrahedron*, 46, 3321 (1990); Bartlett, P.A. in *Asymmetric Synthesis*; Morrison, J.D, Ed.; Academic Press, New York, vol. 3 (1984), p. 411; Hegedus, L.S. *Tetrahedron*, 40, 2415 (1984); Gasc, M.B.; Lattes, A. and Perie, J.J. *Ibid.*, 39, 703 (1983).

16 Brunner, H. *Synthesis*, 645 (1988); Brunner, H. *Top. Stereochem.*, 18, 129 (1988); Morrison, J.D., Ed. *Asymmetric Synthesis*; Academic Press, Orlando, FL, vol. 5 (1985); ApSimon, J.W. and Collier, T.L. *Tetrahedron*, 42, 5157 (1986).

17 Rossiter, B.E. in *Asymmetric Synthesis*, Morrison, J.D., Ed.; Academic Press, Orlando, FL, vol. 5 (1985), p. 193.

18 Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H. and Sharpless, K.B. *J. Am. Chem. Soc.*, 109, 5765 (1987).

19 Page, P.C.B.; Rayner, C.M. and L. Sutherland, I.O. *J. Chem. Soc., Chem. Commun.*, 1408 (1986); Izawa, T; Wang, Z.; Nishimura, Y.; Kondo, S. and Umezawa, H. *Chem. Lett.*, 1655 (1987).

20 Finn, M.G. and Sharpless, K.B. in *Asymmetric Synthesis*, Morrison, J.D., Ed.; Academic Press, Orlando, FL, vol. 5 (1985), p. 247.

21 Richards, D.R.; Kung, H.H. and Sachtler, W.M.H. *J. Mol. Catal.*, 36, 329 (1986).

22 a)Tomioka, K.; Nakajima, M. and Koga, K. *J. Am. Chem. Soc.*, 109, 6213 (1987)
b)Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G. and Sharpless, K.B. *J. Am. Chem. Soc.*, 110, 1968, (1988)
c)Corey, E.J.; DaSilva Jardine, P.; Virgil, S.; Yuen, P.-W. and Connell, R.D. *J. Am. Chem. Soc.*, 111, 9243 (1989).

23 a)Knowles, W.S. *J. Chem. Educ.*, 63, 222 (1986)
b)Halpern, J. in *Asymmetric Synthesis*, Morrison, J.D., Ed.; Academic Press, Orlando, FL, vol. 5 (1985), p. 41.

24 Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. and Weinkauff, D.J. *J. Am. Chem. Soc.*, 97, 2567 (1975).

25 Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.;

Kasahara, I. and Noyori, R. *Ibid.*, 109, 1596 (1987)

26 a)Auburn, P.R.; Mackenzie, P.B. and Bosnich, B. *Ibid.*, 107, 2033 (1985).
b)Mackenzie, P.B.; Whelan, J. and Bosnich, B. *Ibid.*, 107, 2046 (1985).

27 Consiglio, G. and Waymouth, R.M. *Chem. Rev.*, 89, 257 (1989)

28 Hayashi, T.; Yamamoto, A.; Hagihara, T.; and Ito, Y. *Tetrahedron Lett.*, 27, 191 (1986)

29 Hayashi, T. and Kumada, M. *Acc. Chem. Res.*, 15, 395 (1982)

30 Ojima, I. and Hirai, K. in *Asymmetric Synthesis*, Morrison, J.D., Ed.; Academic Press, Orlando, FL, vol. 5 (1985), p. 103.

31 Kollar, L.; Consiglio, G. and Pino, P. *J. Organomet. Chem.*, 330, 305 (1987).

32 Parrinello, G. and Stille, J.K. *J. Am. Chem. Soc.*, 109, 7122 (1987)

33 Cometti, G. and Chiusoli, G.P. *J. Organomet. Chem.*, 236, C31 (1982).

34 a)Alper, H. and Hamel, N. *J. Chem. Soc., Chem. Commun.*, 135 (1990).
b)Alper, H. and Hamel, N. *J. Am. Chem. Soc.*, 112, 2803 (1990).

35 Backvall, J.-E.; Bjorkman, E.E. and Bystrom, S.E. *Tetrahedron Lett.*, 23, 943 (1982).

36 Soai, K.; Hayasaka, T. and Ugajin, S. *J. Chem. Soc., Chem. Commun.*, 516 (1989)

37 Brunner, H. A*dv. Organomet. Chem.*, 18, 151 (1980)

38 Alt, H.; Herberhold, M.; Kreiter, C.G. and Strack, H. *J. Organomet. Chem.*, 102, 491 (1975).

39 Werner, H. and Feser, R. *Ibid.*, 232, 351 (1982).

40 a)Kiel, W.A.; Lin, G.-Y.; Bodner, G.S. and Gladysz, J.A. *J. Am. Chem. Soc.*, 105, 4958 (1983).
b)Bodner, G.S.; Fernandez, J.M.; Arif, A.M. and Gladysz, J.A. *Ibid.*, 110, 4082 (1988).

41 Boucher, H. and Bosnich, B. *Ibid.*, B. 99, 6253 (1977).

42 Panunzi, A. and Paiaro, G. *Ibid.*, 88, 4843 (1966).

43 Shimoda, S.; Yamaguchi, Y. and Saito, Y. *Inorg. Chem.*, 18, 673 (1979).

44 De Renzi, A.; Di Blasio, B; Saporito, A; Scalone, M. and Vitagliano, A. *Ibid.*, 19, 960 (1980).

45 van der Poel, H. and van Koten, G. *Ibid.*, 20, 2950 (1981).

46 a)Consiglio, G.; Pregosin, P. and Morandini, F. *J. Organomet. Chem.*, 308, 345 (1986).
b)Consiglio, G. and Morandini, F. *Ibid.*, 310, C66 (1986).

47 a)Lazzaroni, R.; Uccello-Barretta, G.; Bertozzi, S.; Bertucci, C. and Marchetti, F. *J. Chem. Res. (S)*, 286 (1984).

48 Uccello-Barretta, G.; Lazzaroni, R.; Bertucci, C. and Salvadori, P. *Organometallics*, 6, 550 (1987).

49 Farrar, D.H.. and Payne, N.C. *J. Am. Chem. Soc.*, 107, 2054 (1985).

50 Brown, J.M. and MacIntyre, J.E. *J. Chem. Soc. Perkin Trans. 2*, 961 (1985).

51 a)McCrindle, R.; Alyea, E.C.; Ferguson, G.; Dias, S.A.; McAlees, A.J. and Parvez, M. *J. Chem. Soc., Dalton Trans.*, 137 (1980).
b)Ratnayake Bandara, B.M.; Birch, A.J. and Raverty, W.D. *J. Chem. Soc., Perkin Trans. 1*, 1755 (1982).
c)Cupertino, D.C.; Harding, M.M. and Cole-Hamilton, D.J. *J. Organomet. Chem.*, 294, C29 (1985).
d)Preston, S.A.; Cupertino, D.C.; Palma-Ramirez, P. and Cole-Hamilton, D.J. *J. Chem. Soc., Chem. Commun.*, 977 (1986).
e)Krafft, M.E.; Wilson, L.J. and Onan, K.D. *Tetrahedron Lett.*, 29, 6421 (1988).
f)Krafft, M.E. *Ibid.*, 30, 539 (1989).

52 Semmelhack, M.F.; Bodurow, C. and Baum, M. *Ibid.*, 25, 3171 (1984).

53 Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H. and Yoshida, Z. *Ibid.*, 26, 4479 (1985).

54 Sharpless, K.B. and Michaelson, R.C. *J. Am. Chem. Soc.*, 95, 6136 (1973).

55 Chamberlin, A.R.; Mulholland, R.L., Jr.; Kahn, S.D. and Henre, W.J. *Ibid.*, 109, 672 (1987).

56 Vara Prasad, J.V.N. and Pillai, C.N. *J. Organomet. Chem.*, 259, 1 (1983).

57 Brown, J.M. *Angew. Chem. Int. Ed. Engl.*, 26, 190 (1987).

58 Eisch, J.J. *J. Organomet. Chem.*, 200, 101 (1980).

59 Eisch, J.J.; Merkley, J.H. and Galle, J.E. *J. Org. Chem.*, 44, 587 (1979).

60 Evans, D.A.; Morrissey, M.M. and Dow, R.L. *Tetrahedron Lett.*, 26, 6005 (1985).

61 Holton, R.A. *J. Am. Chem. Soc.*, 99, 8083 (1977).

62 Heumann, A.; Reglier, M. and Waegell, B. *Angew. Chem. Int. Ed. Engl.*, 21, 366 (1982).

63 Hines, L.F. and Stille, J.K. *J. Am. Chem. Soc.*, 94, 485 (1972).

64 Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C. and Bass, L.S. *Ibid.*, 106, 2458 (1984).

65 Burke, S.D. and Cobb, J.E. *Tetrahedron Lett.*, 27, 4237 (1986).

66 Breslow, R. and Heyer, D. *J. Am. Chem. Soc.*, 104, 2045 (1982).

67 Collum, D.B.; DePue, R.T. and Klang, J.A. *Organometallics*, 5, 1015 (1986).

68 DePue, R.T.; Collum, D.B.; Ziller, J.W. and Churchill, M.R. *J. Am. Chem. Soc.*, 107, 2131 (1985).

69 Zhang, W.-Y.; Jakiela, D.J.; Maul, A.; Knors, C.; Lauher, J.W.; Helquist, P. and Enders, D. *Ibid.*, 110, 4652 (1988).

70 Brocard, J.; Lebibi, J.; Pelinski, L. and Mahmoudi, M. *Tetrahedron Lett.*, 27, 6325 (1986).

71 Lazzaroni, R.; Salvadori, P. and Pino, P. *J. Chem. Soc., Chem. Commun.*, 1164 (1970).

72 Ammendola, P.; Ciajolo, M.R.; Panunzi, A. and Tuzi, A. *J. Organomet. Chem.*, 254, 389 (1983).

73 For reviews on the interaction of chiral allenes with electrophiles see:
a)Smadja, W. *Chem. Rev.*, 83, 263 (1983).
b)Jacobs, T.L. in *The Chemistry of the Allenes*, Landor, S.R., Ed.; Academic Press, New York, vol. 2 (1982), p.349.

The interaction of allene with platinum(II) coordinated by a chiral biphosphine ligand has been reported. Brown, J.M.; Cook, S.J. and Kimber, S.J. *J. Organomet. Chem.*, 269, C58 (1984).

74 a)Walkup, R.D. and Park, G. *J. Am. Chem. Soc.*, 112, 1597 (1990).
b)Gallagher, T. *J. Chem. Soc., Chem. Commun.*, 1554 (1984).

75 Kinsman, R.; Lathbury, D.; Vernon, P. and Gallagher, T. *Ibid.*, 243 (1987).

76 Harding, K.E. and Marman, T.H. *J. Org. Chem.*, 49, 2838 (1984).

77 Danishefsky, S.; Taniyama, E. and Webb, R.R. II, *Tetrahedron Lett.*, 24, 11 (1983).

78 For a review, see Bowden, F.L. and Giles, R. *Coord. Chem. Rev.*, 20, 81 (1976).

79 Racanelli, P.; Pantini, G.; Immirzi, A.; Allegra, G. and Porri, L. *J. Chem. Soc., Chem. Commun.*, 361 (1969).

80 For an exception, see:
Kadonaga, M.; Yasuoka, N. and Kasai, N. *Ibid.*, 1597 (1971).

81 Nagendrappa, G.; Joshi, G.C. and Devaprabhakara, D. *J. Organomet. Chem.*, 27, 421 (1971).

82 Powell, J. and Dowling, N.I. *Organometallics*, 2, 1742 (1983).

83 Vrieze, K.; Volger, H.C. and Praat, A.P. *J. Organomet. Chem.*, 21, 467 (1970).

84 Foxman, B.; Marten, D.; Rosan, A.; Raghu, S. and Rosenblum, M. *J. Am. Chem. Soc.*, 99, 2160 (1977).

85 Bhagwat, M.M. and Devaprabhakara, D. *Tetrahedron Lett.*, 15, 1391 (1972).

86 a)Schultz, R.G. *Tetrahedron*, 20, 2809 (1964).
b)Lupin, M.S.; Powell, J. and Shaw, B.L. *J. Chem. Soc. (A)*, 1687 (1966).

87 Briggs, J.R.; Crocker, C.; McDonald, W.S. and Shaw, B.L. *J. Chem. Soc. Dalton Trans.*, 575 (1981).

88 Shimizu, I. and Tsuji, J. *Chem. Lett.*, 233 (1984).

89 Hegedus, L.S.; Kambe, N. Tamura, R. and Woodgate, P.D. *Organometallics*, 2, 1658 (1983).

90 Thebtaranonth, C. and Thebtaranonth, Y. *Tetrahedron*, 46, 1385 (1990) and references therein.

91 Hegedus, L.S.; Allen, G.F. and Olsen, D.J. *J. Am. Chem. Soc.*, 102, 3583 (1980).

92 Clive, D.L.J.; Farina, V.; Singh, A.; Wong, C.K.; Kiel, W.A. and Menchen, S.M. *J. Org. Chem.*, 45, 2120 (1980).

93 Wakabayashi, T.; Kato, Y. and Watanabe, K. *Chem. Lett.*, 1283 (1976).

94 Baldwin, S.W. and Aube, J. *Tetrahedron Lett.*, 28, 179 (1987).

95 Martin, S.F. and Campbell, C.L. *J. Org. Chem.*, 53, 3184 (1988).

96 a) Kinsman, R.; Lathbury,D.; Vernon, P. and Gallagher, T. *J. Chem. Soc., Chem. Commun.*, 243 (1987).
b) Lathbury, D.; Vernon, P. and Gallagher, T. *Tetrahedron Lett.*, 27, 6009 (1986).

97 a) Claesson, A.; Sahlberg, C. and Luthman, K. *Acta. Chem. Scand. B*, 33, 309 (1979).
b) Arseniyadis, S. and Gore, J. *Tetrahedron Lett.*, 24, 3997 (1983).
c) Arseniyadis, S. and Sartoretti, J. *Ibid.*, 26, 729 (1985).
d) For intermolecular palladium(II)-mediated additions to allenes see Alper, H.; Harstock, F.W. and Despeyroux, B. *J. Chem. Soc., Chem. Commun.*, 905 (1984).

98 Coates, R.M.; Senter, P.D. and Baker, W.R. *Ibid.*, 47, 3597 (1982).

99 a) Crandall, J.K. and Tindell, G.L. *J. Chem. Soc., Chem. Commun.*, 1411 (1970).
b) Dauben, W.G. and Shapiro, G. *J. Org. Chem.*, 49, 4252 (1984).

100 Application of a related method for reductive amination employing diborane as the reducing agent offered no improvement in yield of (88). Morales, H.-R.; Perez-Juarez, M.; Cuellar, L.; Mendoza, L.; Fernandez, H. and Contreras, R. *Synth. Commun.*, 14, 1213 (1984).

101 Meyers, A.I.; Poindexter, G.S. and Brich, Z. *J. Org. Chem.*, 43, 892 (1978).

102 For example $[\alpha]_D^{20}$ (phenylglycine methyl ester hydrochloride) -111° (c 1.0, H_2O); Lit. $[\alpha]_D$ -118° (c 1.0, H_2O). Kline, W.; Scpoes, P.M.; Thomas, R.N. and Dahn, H. *Helv. Chim. Acta.*, 54, 2420 (1971).

103 Kaiser, E.M. and McClure, J.R. *J. Organomet. Chem.*, 175, 11 (1979).

104 Naef, R. and Seebach, D. *Helv. Chim. Acta.*, 68, 135 (1985).

105 Karver, P.; Portmann, P. and Suter, M. *Ibid.*, 31, 1617 (1948).

106 Winterfeldt, E. *Synthesis*, 625 (1975).

107 Perrin, D.D. *Stability Constants of Metal-Ion Complexes, part B (organic ligands)*; Pergamon Press, Oxford, (1979).

108 Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S. and Yoshida, Z. *J. Org. Chem.*,

52, 4062 (1987).

109 Nicolaou, K.C.; Magolda, R.L.; Sipio, W.J.; Barnette, W.E.; Lysenko, Z. and Joullie, M.M. *J. Am. Chem. Soc.*, 102, 3784 (1980).

110 Lathbury, D. and Gallagher, T. *J. Chem. Soc., Chem. Commun.*, 114 (1986).

111 Horner, L. and Dickerhof, K. *Liebigs Ann. Chem.*, 1240 (1984).

112 Villani, F.J. Jr., Costanzo, M.J.; Inners, R.R.; Mutter, M.S. and McClure, D.E. *J. Org. Chem.*, 51, 3715 (1986).

113 a) Grundon, M.F.; Stewart, D. and Watts, W.E. *J. Chem. Soc., Chem. Commun.*, 573 (1973).
b) Hosokawa, T.; Okuda, C. and Murahashi, S.-I. *J. Org. Chem.*, 50, 1282 (1985).
c) Heumann, A. and Moberg, C. *J. Chem. Soc., Chem. Commun.*, 1516 (1988).

114 Freifelder, M. *Practical Catalytic Hydrogenation*; Wiley-Interscience, New York, chapter 19 (1971), p. 433.

115 Johnstone, R.A.W.; Wilby, A.H. and Entwistle, I.D. *Chem. Rev.*, 85, 129 (1985).

116 a) Bringmann, G. and Geisler, J.-P. *Tetrahedron Lett.*, 30, 317 (1989).
b) Bieg, T. and Szeja, W. *Synthesis*, 76, (1985).

117 Weir, J.R.; Patel, B.A. and Heck, R.F. *J. Org. Chem.*, 45, 4926 (1980).

118 a) Iimori, T. and Shibasaki, M. *Tetrahedron Lett.*, 26, 1523 (1985).
b) Evans, D.A. and Sjogren, E.B. *Ibid.*, 26, 3783, (1985).

119 Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press, 3rd edition, chapter 7 (1986), p.452.

120 Yoshimura, J.; Yamaura, M.; Suzuki, T. and Hashimoto, H. *Chem. Lett.*, 1001 (1983).

121 Ferris, J.P.; Gerwe, R.D. and Gapski, G.R. *J. Org. Chem.*, 33, 3493 (1968).

122 Monkovic, I; Wong, H. and Bachand, C. *Synthesis*, 770 (1985).

123 Meisenheimer, J. *Chem. Ber.*, 41, 3966 (1908).

124 a) Moriwaki, M.; Sawada, S. and Inouye, Y. *J. Chem. Soc., Chem. Commun.*, 419 (1970).
b) Yamamoto, Y.; Oda, J. and Inouye, Y. *J. Org. Chem.*, 41, 303 (1976).

126 Hobson, J.D. and McCluskey, J.G. *J. Chem. Soc. (C)*, 2015 (1967).

127 Reinecke, M.G. and Daubert, R.G. *J. Org. Chem.*, 38, 3281 (1973).

127 Cooley, J.H. and Evain, E.J. *Synthesis*, 1 (1989).

128 Brandsma, L. and Verkrkuiysse, H.D.; *Synthesis of Acetylenes, Allenes and Cumulenes; Studies in Organic Chemistry*; Elsevier, vol.8 (1981).

129 Parikh, J.R. and Doering W. von E. *J. Am. Chem. Soc.*, 89, 5505 (1967).

130 This amino amide was prepared in racemic form by heating phenylglycine

methyl ester hydrochloride in pyrrolidine in a sealed tube at 100°C for 2h; Griffin, S.J.; Project Report for the Degree in Chemistry, University of Bath (1990).

131 Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J. and Sabel, A. *Angew. Chem. Intl. Ed. Eng*,. 1, 80 (1962).

132 a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag, Berlin (1980).
b) Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic Press, London (1985).

133 For a recent discussion of the mechanism of carbomethoxylation of organopalladium species see Moser, W.R.; Wang, A.W. and Kildahl, N.K. *J. Am. Chem. Soc.*, 110, 2816 (1988).

134 Taura, Y.; Tanaka, M.; Funakoshi, K. and Sakai, K. *Tetrahedron Lett.*, 30, 6349 (1989).

135 Morandini, F.; Consiglio, G. and Piccolo, O. *Inorg. Chim. Acta*, 57, 15 (1982).

136 Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T. and Noyri, R. *J. Am. Chem. Soc.*, 102, 7932 (1980).

137 Hegedus, L.S.; Mulhern, T.A. and Asada, H. *Ibid.*, 108, 6224 (1986).

138 Sen, A. and Lai, T.-W. *Ibid.*, 103, 4627 (1981).

139 Schramm, R.F. and Wayland, B.B. *J. Chem. Soc., Chem. Commun.*, 898 (1968).

140 Lai, T.-W. and Sen, A. *Organometallics*, 3, 866 (1984).

141 Hiroi, K.; Suya, K. and Sato, S. *J. Chem. Soc., Chem. Commun.*, 469 (1986).

142 Fukuda, Y; Utimoto, K. and Nozaki, H. *Heterocycles*, 25, 297 (1987).

143 Whitesides, G.M.; Casey, C.P. and Krieger, J.K. *J. Am. Chem. Soc.*, 93, 1379 (1971).

144 a) Normant, J.F.; Cahiez, G; Chuit, C. and Villieras, J. *J. Organomet. Chem.*, 77, 269 (1974).
b) Ten Hoedt, R.W.M.; Van Koten, G. and Noltes, J.G. *Ibid.*, 201, 327 (1980).

145 a) Perie, J.J.; Laval, J.P.; Roussel, J. and Lattes, A *Tetrahedron*, 28, 675 (1972).
b) Frank, W.C.; Kim, Y.C. and Heck, R.F. *J. Org. Chem.*, 43, 2947 (1978).

146 Barluenga, J.; Alonso-Cires, L. and Asensio, G. *Synthesis*, 962 (1979).

147 a) Stille, J.K. and Wong, P.K. *J. Org. Chem.*, 40, 335 (1975).
b) Harding, K.E. and Burks, S.R. *Ibid.*, 49, 40 (1984).
c) Narayana, C. and Periasamy, M. *Synthesis*, 254 (1985).

148 Waters, W.L. and Kiefer, E.F. *J. Am. Chem. Soc.*, 89, 6261 (1967).

149 Bach, R.D. *Ibid.*, 91, 1771 (1969).

150 a) Rychnovsky, S. and Bartlett, P.A. *Ibid.*, 103, 3963 (1981).
b) Labelle, M.; Morton, H.E; Guindon, Y. and Springer, Y.P. *Ibid.*, 110, 4533

(1988).

151 Larock, R.C. *J. Org. Chem.*, 40, 3237 (1975).

152 Fuchikami, T. and Ojima, I. *Tetrahedron Lett.*, 23, 4099 (1982).

153 Falbe, J. and Korte, F. *Angew. Chem.*, 74, 291 (1962).

154 Yamamoto, T.; Igarashi, K.; Komiya, and Yamamoto, A. *J. Am. Chem. Soc.*, 102, 7448 (1980).

155 Dreiding, A. *Helv. Chim. Acta*, 42, 1339 (1959).

156 Pasto, D.J. and Miles, M.F. *J. Org. Chem.*, 41, 425 (1976).

157 Benhamou, M.C.; Etemad-Moghadam, G.; Speziale, V. and Lattes, A. *Synthesis*, 891 (1979).

158 a)See reference 15 for reviews of non-metal electrophile-mediated cyclisations of unsaturated amines and alcohols.
b) Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S. and Yoshida, X. *J. Org. Chem.*, 52, 4062 (1987).

159 Wong, H.; Chapius, J. and Monkovic, I. *Ibid.*, 39, 1042 (1974).

160 a) Tanaka, O.; Tanaka, N.; Ohsawa, T.; Iitaka, Y. and Shibata, S. *Tetrahedron Lett.*, 4235 (1968).
b) Demole, E. and Enggist, P. *Helv. Chim. Acta*, 54, 456 (1971).

161 Clive, D.L.J.; Farina, V.; Singh, A.; Wong, C.K.; Kiel, W.A. and Menchen, S.M. *J. Org. Chem.*, 45, 2120 (1980).

162 Current, S. and Sharpless, K.B. *Tetrahedron Lett.*, 5075 (1978).

163 Garrat, D.G.; Bealieu, P.L.; Morisset, V.M. and Ujjainwalla, M. *Can. J. Chem.*, 58, 2745 (1980).

164 Johnson, W.S.; Werthemann, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.; Faulkner, D.J. and Peterson, M.R. *J. Am. Chem. Soc.*, 92, 741 (1970).

165 Von Braun, J. *Chem. Ber.*, 33, 1438 (1900).

166 Huisgen, R. and Ruchardt, C. *Liebigs Ann. Chem.*, 601, 21 (1956).

167 Brown, H.C. and Geoghegan, P. Jr. *J. Am. Chem. Soc.*, 89, 1523 (1967).

168 a) Brown, H.C. and Hammar, W.J. *Ibid.*, 89, 1524 (1967).
b)Pasto, D.J. and Gontarz, J.A. *Ibid.*, 92, 7480 (1970).
c)Jasserand, D.; Girard, J.P.; Rossi, J.C. and Granger, R. *Tetrahedron*, 32, 1535 (1976).
d)Senda, Y. Kamiyama, S. and Imaizumi, S. *J. Chem. Soc., Perkins Trans 1*, 530 (1978).

169 Dale, J.A.; Dull, D.L. and Mosher, H.S. *J. Org. Chem.*, 34, 2543 (1969).

170 a) Luo, F.-T. and Negishi, E. *Ibid.*, 48, 5144 (1983).
b) Zhang, Y.; Miller, J.A. and Negishi, E. *Ibid.*, 54, 2043 (1989).
c) Negishi, E.; Zhang, Y. and Bagheri, V. *Tetrahedron Lett.*, 28, 5793 (1987).

d) Wu, G.; Cederbaum, F.E. and Negishi, E. *Ibid.*, 31, 493 (1990).

171 Nugent, W.A.; Thorn, D.L. and Harlow, R.L. *J. Am. Chem. Soc.*, 109, 2788 (1987).

172 a) Garner, P. and Ramakanth, S. *J. Org. Chem.*, 52, 2629 (1987).
b) Rehwinkel, H.; Skupsch, J. and Vorburggen, H. *Tetrahedron Lett.*, 29, 1775, (1988).
c) Harmat, N.J.S. and Warren, S. *Ibid.*, 31, 2743 (1990).

173 Munt, S.P. and Thomas, E.J . *J. Chem. Soc., Chem. Commun.*, 480 (1989).

174 Preliminary studies indicated that this thermodynamic preference does indeed exist; treatment of the *O*-acetyl aldol mixture with potassium hydride led to only E-enelactam formation. Lathbury, D. unpublished results.

175 a) Jones, A.B.; Yamaguchi, M.; Patten, A.; Danishefsky, S.J.; Ragan, J.A.; Smith, D.B. and Schreiber, S.L. *J. Org. Chem.*, 54, 17 (1989).
b) Mitchell, D. and Liebeskind, L.S. *J. Am. Chem. Soc.*, 112, 291 (1990).

176 Bouffard, F.A.; Johnston, D.B.R. and Christensen, B.G. *J. Org. Chem.*, 45, 1130 (1980).

177 Furst, A. and Koller, F. *Helv. Chim. Acta*, 30, 1454 (1947).

178 Thielke, D.; Wegener, J. and Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.*, 13, 602 (1974).

179 Dubois, J.E. and Dubois, M. *J. Chem. Soc., Chem. Commun.*, 1567 (1968).

180 Gawley, R.E.; Termine, E.J. and Aube, J. *Tetrahedron Lett.*, 21, 3115 (1980).

181 Albers-Schonberg, G.; Arison, B.H.; Hensens, O.D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E.A.; Rhodes, R.E.; Kahan, J.S.; Kahan, F.M.; Ratcliffe, R.W.; Walton, E.; Ruswinkle, L.J.; Morin, R.B. and Christensen, B.G. *J. Am. Chem. Soc.*, 100, 6491 (1978).

182 a) Peterson, D.J. *J. Org. Chem.*, 33, 780 (1968).
b) Ager, D.J. *Synthesis*, 384 (1984).

183 Hart, D.J.; Cain, P.A. and Evans, D.A. *J. Am. Chem. Soc.*, 100, 1548 (1978).

184 Kano, S.; Ebata, T.; Funaki, K. and Shibuya, S. *Synthesis*, 746 (1978).

185 Matsui, S. *Bull. Chem. Soc. Jpn.*, 60, 1853 (1987).

186 Larson, G.L.; Cruz de Maldonado, V.; Fuentes, L.M. and Torres, L.E. *J. Org. Chem.*, 53, 633 (1988).

187 Woodbury, R.P. and Rathke, M.W. *Ibid.*, 43, 881 (1978).

188 Evans, D.A.; Takacs, J.M. and Hurst, K.M. *J. Am. Chem. Soc.*, 101, 371 (1979).

189 Bassindale, A.R.; Ellis, R.J.; Lau, J.C.-Y. and Taylor, P.G. *J. Chem. Soc., Perkin Trans. 2*, 593 (1986).

190 Bailey, W.J. and Bird, C.N. *J. Org. Chem.*, 42, 3895 (1977).

191 Hofle, G.; Steglich, W. and Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.*, 17, 569 (1978).

192 Corey, E.J.; Anderson, N.H.; Carlson, R.M.; Paust, J.; Vedejs, E.; Vlattas, I. and Winter, R.E.K. *J. Am. Chem. Soc.*, 90, 3245 (1968).

193 Alexandre, C. and Rouessac, F. *Bull. Soc. Chim. Fr.*, 1837 (1971).

194 Schmidt, E. and Moosmuller, F. *Liebigs Ann. Chem.*, 597, 235 (1955).

195 Torii, S.; Inokuchi, T.; Oi, R; Kazumi, K. and Kobayashi, T. *J. Org. Chem.*, 51, 254 (1986).

196 Schmidt, E.; Dabritz, E.; Thulke, K. and Grassman, E. *Liebigs Ann. Chem.* 685, 161 (1965). For a review of reactions of carbodiimides with alcohols see; Mikolajczyk, M. and Kielbasinski, P. *Tetrahedron*, 37, 233 (1981).

197 Kato, M. and Mori, K. *Agric. Biol. Chem.*, 49, 2479 (1985)

198 a) Evans, D.A.; Ennis, M.D. and Mathre, D.J. *J. Am. Chem. Soc.*, 104, 1737 (1982).
b) Evans, D.A.; Bartroli, J. and Shih, T.L. *Ibid.*, 103, 2127 (1981).

199 This was readily prepared by addition of a solution of phosgene in toluene to commercially available (1S, 2R)-norephedrine: Newman, M.S. and Kutner, A. *Ibid.*, 73, 4199 (1951).

200 Prepared by methylation of the *N*-cyclohexylimine of hexanal followed by reduction ($LiAlH_4$); Lathbury, D. (unpublished work).

201 Schreiber, J. and Eschenmoser, A. *Helv. Chim. Acta*, 38, 1529 (1955).

202 Burgess, E.M.; Penton, H.R., Jr. and Taylor, E.A. *J. Org. Chem.*, 38, 26 (1973).

203 a) Crowell, T.I.; Wall, A.A.; Kemp, R.T. and Lutz, R.E. *J. Am. Chem. Soc.*, 85, 2521 (1963).
b) Buss, A.D.; Warren, S.; Leake, J.S. and Whitham, G.H. *J. Chem. Soc., Perkin Trans. 1*, 2215 (1983).

204 House, H.O.; Crumrine, D.S.; Teranishi, A.Y. and Olmstead, H.D. *J. Am. Chem. Soc.*, 95, 3310 (1973).

205 Borch, R.F. *Tetrahedron Lett.*, 61 (1968).

206 Jorgenson, M.J. *Ibid.*, 559 (1962).

207 Yoon, N.M. and Brown, H.C. *J. Am. Chem. Soc.*, 90, 2927 (1968).

208 Lyle, G.G. and Lyle, R.E. in *Asymmetric Synthesis*, Morrison, J.D., Ed.; Academic Press, New York, vol. 1 (1983), p.13.

209 Ohmiya, S.; Kubo, H.; Otomasu, H.; Saito, K. and Muraskoshi, I. *Heterocycles*, 30, 537 (1990).

210 Nagao, Y.; Dai, W-M; Ochiai, M.; Tsukagoshi, S. and Fiyita, E. *J. Org. Chem.*, 55, 1149 (1990).

211 The optical rotation of *ent*-(77), $[\alpha]_D^{19}$ +60.8° (c 1.2, $CHCl_3$), was significantly

lower than expected on the basis of that obtained for the enantiomer {$[\alpha]_D^{20}$ -98.3° (c 1.2, $CHCl_3$)}. A possible explanation for this discrepancy is that the latter was determined using material additionally purified by bulb-to-bulb distillation.

212 Lane, C.F. *J. Org. Chem.*, 39, 1436 (1955).

213 Literature value[210] $[\alpha]_D^{22}$ -25.9° (c 1.16, EtOH). The low value observed could be due to inaccuracies associated with optical rotation determinations of small samples. Alternatively, partial racemisation during the epimerisation step, *via* a retro-aza-Michael pathway, might be responsible.

214 Perrin, D.D. and Armarego, W.L.F. *Purification of Laboratory Chemicals*; Pergamon Press, Oxford, 3rd edition (1988).

APPENDIX

X-Ray Crystal Data

1. The hydrochloride salt **(114)** (Figure 7) crystallised (dichloromethane/ethyl acetate/cyclohexane) in space group $P2_12_12_1$ with a = 10.818(5), b = 13.841(4), c = 15.198(4)Å, U = 2271.3Å^3, and D_c = 1.231gcm^{-3} for Z = 4 at room temperature. The structure was solved by direct methods using 1198 unique reflections with $I \geq 3\sigma I$ and refined by full matrix least squares to final residues of R = 7.49% for unit weights.

2. The E-enelactam E-**(74)** (Figure 8) crystallised (dichloromethane/petrol) in space group $P2_12_12_1$ with a = 5.819(2), b = 11.256(2), c = 24.471(4)Å, U = 1602.9Å^3, and D_c = 1.1 gcm^{-3} for Z = 4 at room temperature. The structure was solved by direct methods using 946 unique reflections with $I \geq 3\sigma I$ and refined by full matrix least squares to final residuals of R = 9.30% for unit weights.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

PUBLICATIONS

PUBLICATIONS

1. **Asymmetric Synthesis of Functionalised Pyrrolidines. The Role of a Stereogenic Centre on Nitrogen.**
   J. Chem. Soc., Chem. Commun., 1073 (1989).

2. **Asymmetric Synthesis *via* Electrophile-Mediated Cyclisations.**
   Tetrahedron, 46, 4697 (1990).

3. **Enantioselective Synthesis of Pumiliotoxin 251D. A Strategy Employing an Allene-Based Electrophile-Mediated Cyclisation.**
   J. Am. Chem. Soc. (in press).

AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF PUMILIOTOXIN 251D

Submitted by David Nathan Abraham Fox

for the degree of Ph.D.

of the University of Bath

1990

INTRODUCTION

RESULTS AND DISCUSSION

EXPERIMENTAL

REFERENCES

APPENDIX

PUBLICATIONS

PUBLISHED PAPERS NOT FILMED FOR COPYRIGHT REASONS

pages - 231, 232